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## Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life (Review)

Gates NJ, Rutjes AWS, Di Nisio M, Karim S, Chong LY, March E, Martínez G, Vernooij RWM

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# Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life

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## ABSTRACT

### Background

Increasing age is associated with a natural decline in cognitive function and is also the greatest risk factor for dementia. Cognitive decline and dementia are significant threats to independence and quality of life in older adults. Therefore, identifying interventions that help to maintain cognitive function in older adults or to reduce the risk of dementia is a research priority. Cognitive training uses repeated practice on standardised exercises targeting one or more cognitive domains and is intended to maintain optimum cognitive function. This review examines the effect of computerised cognitive training interventions lasting at least 12 weeks on the cognitive function of healthy adults aged 65 or older.

### Objectives

To evaluate the effects of computerised cognitive training interventions lasting at least 12 weeks for the maintenance or improvement of cognitive function in cognitively healthy people in late life.

### Search methods

We searched to 31 March 2018 in ALOIS ([www.medicine.ox.ac.uk/alois](http://www.medicine.ox.ac.uk/alois)) and performed additional searches of MEDLINE, Embase, PsycINFO, CINAHL, ClinicalTrials.gov, and the WHO Portal/ICTRP ([www.apps.who.int/trialsearch](http://www.apps.who.int/trialsearch)) to ensure that the search was as comprehensive and as up-to-date as possible, to identify published, unpublished, and ongoing trials.

### Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs, published or unpublished, reported in any language. Participants were cognitively healthy people, and at least 80% of the study population had to be aged 65 or older. Experimental interventions adhered to the following criteria: intervention was any form of interactive computerised cognitive intervention - including computer exercises, computer games, mobile devices, gaming console, and virtual reality - that involved repeated practice on standardised exercises

of specified cognitive domain(s) for the purpose of enhancing cognitive function; duration of the intervention was at least 12 weeks; cognitive outcomes were measured; and cognitive training interventions were compared with active or inactive control interventions.

### **Data collection and analysis**

We performed preliminary screening of search results using a 'crowdsourcing' method to identify RCTs. At least two review authors working independently screened the remaining citations against inclusion criteria. At least two review authors also independently extracted data and assessed the risk of bias of included RCTs. Where appropriate, we synthesised data in random-effect meta-analyses, comparing computerised cognitive training (CCT) separately with active and inactive controls. We expressed treatment effects as standardised mean differences (SMDs) with 95% confidence intervals (CIs). We used GRADE methods to describe the overall quality of the evidence for each outcome.

### **Main results**

We identified eight RCTs with a total of 1183 participants. Researchers provided interventions over 12 to 26 weeks; in five trials, the duration of intervention was 12 or 13 weeks. The included studies had a moderate risk of bias. Review authors noted a lot of inconsistency between trial results. The overall quality of evidence was low or very low for all outcomes.

We compared CCT first against active control interventions, such as watching educational videos. Because of the very low quality of the evidence, we were unable to determine any effect of CCT on our primary outcome of global cognitive function or on secondary outcomes of episodic memory, speed of processing, executive function, and working memory.

We also compared CCT versus inactive control (no interventions). Negative SMDs favour CCT over control. We found no studies on our primary outcome of global cognitive function. In terms of our secondary outcomes, trial results suggest slight improvement in episodic memory (mean difference (MD) -0.90, 95% confidence interval (CI) -1.73 to -0.07; 150 participants; 1 study; low-quality evidence) and no effect on executive function (SMD -0.08, 95% CI -0.31 to 0.15; 292 participants; 2 studies; low-quality evidence), working memory (MD -0.08, 95% CI -0.43 to 0.27; 60 participants; 1 study; low-quality evidence), or verbal fluency (MD -0.11, 95% CI -1.58 to 1.36; 150 participants; 1 study; low-quality evidence). We could not determine any effects on speed of processing at trial endpoints because the evidence was of very low quality.

We found no evidence on quality of life, activities of daily living, or adverse effects in either comparison.

### **Authors' conclusions**

We found little evidence from the included studies to suggest that 12 or more weeks of CCT improves cognition in healthy older adults. However, our limited confidence in the results reflects the overall quality of the evidence. Inconsistency between trials was a major limitation. In five of the eight trials, the duration of intervention was just three months. The possibility that longer periods of training could be beneficial remains to be more fully explored.

## **PLAIN LANGUAGE SUMMARY**

### **Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life**

#### **Background**

The terms 'cognition' and 'cognitive function' describe all of the mental activities related to thinking, learning, remembering, and communicating. There are normal changes in cognition with aging. There are also diseases that affect cognition, principally dementia, which becomes increasingly common with increasing age from about 65 years onwards. Researchers have showed a great deal of interest in trying to prevent cognitive decline and dementia. It is known that being mentally active throughout life is associated with lower risk of dementia. Therefore, it has been suggested that encouraging mental activity might be an effective way of maintaining good cognitive function as people age. Cognitive training comprises a set of standardised tasks intended to 'exercise the brain' in various ways. Programmes of cognitive training are often delivered by computers or mobile technology, so that people can do this training on their own at home. Increasingly, these are available as commercial packages that are advertised to the general public. We wanted to know whether computerised cognitive training (CCT) is an effective way for people aged 65 and older to maintain good cognitive function as they age.

#### **What we did**

We searched the medical literature up to 15 March 2018 for trials that compared the cognitive function of people aged 65 or older who had taken part in computerised cognitive training lasting at least three months against a control group that had not done so. All participants should have been cognitively healthy at the start of the trials. For the comparison to be as fair as possible, it should have been decided randomly whether participants were in the cognitive training group or in the control group. We were primarily interested in overall measures of cognition. The choice of three months for the intervention was somewhat arbitrary, but we thought it unlikely that shorter periods of training could have long-lasting effects.

### **What we found**

We found eight trials with a total of 1183 participants to include in the review. Four trials provided CCT for three months. The longest duration of training was six months. We compared CCT with other activities, such as watching educational videos, and with no activity at all. We looked for effects on overall cognitive function and on specific cognitive functions, such as memory and thinking speed. All of the studies had some design problems, which could have biased the results. Results show a lot of inconsistency between different trials. Overall, we thought the quality of the evidence found was low or very low. This means that we cannot be confident in the results, and that more research might well find something different. We either were unable to comment or found no evidence of an effect of CCT on overall cognitive function or on most of the specific cognitive functions that we examined. The longest trial also found that compared to doing nothing, completing six months of CCT may have had a beneficial effect on memory. None of the trials reported effects on quality of life or on daily activities, and none reported harmful effects of training.

### **Our conclusions**

It is not yet possible to say for certain whether or not computerised cognitive training can help older people to maintain good cognitive function. Although we excluded very short trials (< 3 months) from this review, the trials that we found were still quite short for examining long-term effects as people age. We think it is important to do more research to find out whether longer periods of training work better, and whether training can produce lasting effects.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Computerised cognitive training compared with active control intervention in cognitively healthy people in late life				
<b>Patient or population:</b> cognitively healthy people in late life <b>Settings:</b> general population <b>Intervention:</b> computerised cognitive training <b>Comparison:</b> active control intervention				
Outcomes	Difference between CCT and control (95% CI)*	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Global cognitive function measured at the end of follow-up	SMD 1.06 lower (2.73 lower to 0.61 higher)	198 participants (2 studies)	⊕○○○ very low <sup>b</sup>	It is uncertain whether CCT maintains global cognitive function better than active control
Cognitive subdomain: episodic memory measured at the end of follow-up	SMD 0.18 lower (1.00 lower to 0.64 higher)	439 participants (4 studies)	⊕○○○ very low <sup>b</sup>	It is uncertain whether CCT maintains episodic memory better than active control
Cognitive subdomain: speed of processing measured at the end of follow-up	SMD 0.63 lower (1.14 lower to 0.12 lower)	138 participants (2 studies)	⊕○○○ very low <sup>b</sup>	It is uncertain whether CCT maintains speed of processing better than active control
Cognitive subdomain: executive functioning measured at the end of follow-up	SMD 0.34 lower (1.45 lower to 0.77 higher)	230 participants (3 studies)	⊕○○○ very low <sup>b</sup>	It is uncertain whether CCT maintains executive functioning better than active control
Cognitive subdomain: working memory measured at the end of follow-up	SMD 1.01 lower (2.45 lower to 0.53 higher)	392 participants (3 studies)	⊕○○○ very low <sup>b</sup>	It is uncertain whether CCT maintains working memory better than active control
Quality of life	Not reported using a validated measure			
Number of participants experiencing 1 or more serious adverse events	Not reported using a validated measure			

\* The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CCT: computerised cognitive training; CI: confidence interval; SMD: standardised mean difference

GRADE Working Group grades of evidence.

**High quality:** further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** we are very uncertain about the estimate.

<sup>a</sup>The direction of the difference in effect was standardised so that lower values favour CCT and higher values favour control.

<sup>b</sup>Downgraded three levels for imprecision (confidence interval included effects that are not clinically relevant), inconsistency (high heterogeneity), and risk of bias.

## BACKGROUND

### Description of the condition

#### Cognitive health, dementia, and reserve

'Cognitive health' broadly refers to the absence of cognitive impairment and the preservation of cognitive structure. Maintaining cognitive health in later life is essential to allow older adults to achieve active ageing (Depp 2012; Hendrie 2006). 'Active ageing' refers to the process of optimising opportunities for health, participation, and security in later life (WHO 2016). Older adults themselves are increasingly interested in managing their own health and have expectations of positive ageing and a high quality of life (Brown 2004). Retirement age in many countries is being extended past age 65, and many older adults want to extend their working lives, requiring them to maintain cognitive health as long as possible. Cognitive decline and dementia are significant threats to independence and active ageing, and are significant concerns of older adults (Deary 2009; Lustig 2009).

Dementia is now one of the biggest global health challenges and may affect up to 135 million adults worldwide by 2050 (Prince 2013). The global cost of caring for people with dementia is currently estimated at USD315 billion (Wimo 2010). The World Health Organization 2017 Dementia Action Plan identifies reducing dementia risk as a major health objective (who.int/mental\_health/neurology/dementia/action\_plan\_2017\_2025/en/). In most cases, the onset of clinical dementia is gradual, with the underlying disease process probably starting years, or even decades, before symptoms present. Pharmacological treatments at present are very limited, and none are curative (Aisen 2011). The long prodromal and preclinical periods before dementia onset offer an opportunity to intervene to maintain cognitive function, thereby preventing or postponing the onset of clinical dementia (Leifer 2003). Postponing the onset of clinical dementia by just five years could potentially reduce disease prevalence by 50% (Brookmeyer 1998). Differences in individual susceptibility to the development of clinical dementia may in part be due to exposure to a number of positive and negative factors. Multiple potentially modifiable factors have been identified, including physical exercise, diet, and mentally stimulating activities (World Alzheimer Report 2014). Accordingly, new non-pharmacological lifestyle interventions are being investigated for their potential to prevent or delay dementia onset (Acevedo 2007; Dresler 2013).

Research evidence indicates that maintenance of cognitive health requires the development of optimal levels of brain and cognitive reserve across the lifespan (Stern 2012). 'Brain reserve' refers to structural tolerance of the brain to disease processes. 'Cognitive reserve' refers to functional differences in cognitive processes that may affect the way cognitive tasks are performed, which may in turn enhance resilience against threats to cognitive health. Thus,

reserve provides a theoretical explanation for the differences between individuals with the same degree of disease in the brain who succumb to clinical dementia and are functionally impaired, and those who tolerate the pathology and maintain function (Stern 2012). Consistent with this notion of reserve is evidence from epidemiological and prospective studies that a lower incidence of Alzheimer's disease is found in people who have engaged in mentally stimulating activities (Marioni 2014; Marquine 2012; Stern 2012; Verghese 2003; Wilson 2002). Therefore, one intervention that has been proposed to increase cognitive health and improve cognitive function in older adults is the introduction of novel mental activity (Park 2007).

#### Age-related cognitive decline

In cognitively healthy adults, some non-pathological changes in cognitive function naturally occur with increasing age (Salthouse 2003). Cognitive changes associated with normal ageing may contribute to deterioration in quality of life and may compromise functional capacity. Large variations in cognitive health and function are observed at a population level, and trajectories of decline are highly variable (Salthouse 2011). Cross-sectional and longitudinal comparisons indicate that whilst acquired knowledge generally increases until about age 60, there is a decrease in information processing efficiency from early adulthood, and beyond age 60 increasing age is associated with general negative cognitive change (Salthouse 2011). When cognitive difficulties are beyond those associated with normal ageing, but performance of daily activities is not significantly affected, the term 'mild cognitive impairment' (MCI), or its synonym 'mild neurocognitive disorder', is applied. MCI is associated with an increased risk of progression to dementia (Petersen 2018).

#### Risk and protective factors

Although increasing age is the greatest risk factor for dementia, additional risk and protective factors have been linked with dementia in general, and with Alzheimer's disease in particular (World Alzheimer Report 2014). It has recently been suggested that after accounting for non-independence between risk factors, around a third of cases of dementia due to Alzheimer's disease worldwide might be attributable to potentially modifiable risk factors (Norton 2014). Accordingly, there is growing interest in addressing lifestyle factors to combat age-related cognitive decline, enhance cognitive function, and prevent the onset of clinical dementia (Barnes 2011; Dresler 2013). Addressing preventable risks, such as promoting cognitively stimulating activities, is a global health priority according to the World Health Organization 2017 Health Report Dementia Action Plan.

The links between stimulating leisure pursuits and cognitive health are strong. Epidemiological evidence indicates that the risk of developing dementia due to Alzheimer's disease is significantly reduced in individuals with higher educational or occupational at-



tainment (Marioni 2012; Marquine 2012; Stern 2012). Cognitive lifestyle variables such as education, midlife occupation, and late life social engagement may also be associated with cognitive trajectories and morbidity (Marioni 2012; Marioni 2014). A broad spectrum of activities, including those with mental, physical, and social components, contribute to reducing risk for dementia (Karp 2006). Prospective studies also indicate that mental activity, even when commenced late in life, has positive benefits, with lowered rates of decline and lowered dementia incidence reported (Beydoun 2014; Geda 2012; Verghese 2003; Wilson 2002; Wilson 2012). In contrast, lack of cognitive stimulation, particularly across an individual's life course, is a significant risk factor (Norton 2014; World Alzheimer Report 2014). Therefore, introducing cognitively stimulating interventions - even in late life - has the potential to reverse the effects of reduced participation, promote cognitive health and active ageing, and improve quality of life (Amoyal 2012).

## Description of the intervention

Cognitive interventions are diverse treatments based upon the distinct theoretical constructs of maintenance and improvement for the purposes of preventing decline, restoring reduced function, and compensating for impairment (Gates 2014). The clinical research literature refers to three forms of cognitive intervention based upon these theoretical models: cognitive training, cognitive stimulation, and cognitive rehabilitation (Baher-Fuchs 2013; Clare 2004; Gates 2014; Woods 2012).

Cognitive training is increasingly being applied in research and clinical settings for prevention of cognitive decline, and commercial training packages are widely available. 'Cognitive training' is defined as an intervention consisting of repeated practice on standardised exercises, targeting a specific cognitive domain or domains, for the purpose of benefiting cognitive function (Gates 2010). In cognitively healthy older adults, it is intended to maintain cognitive function, reduce age-related decline, and prevent or delay the development of clinical dementia. Recent investigations suggest that cognitive training may improve cognitive function (Petersen 2018). Computer-based cognitive training tasks, including exercises, games, and virtual reality, offer highly accessible, low-cost, standardised interventions.

Several meta-analyses and randomised clinical trials of cognitive training in cognitively healthy adults and those at risk of dementia have reported significant benefits across multiple cognitive domains, global cognition, and composite measures of cognitive function (Alves 2013; Kelly 2014; Kueider 2012; Lampit 2014; Shao 2015). Other meta-analyses of cognitive interventions in longitudinal trials have indicated that such interventions may reduce the risk of developing dementia and may reduce the rate of cognitive decline (Valenzuela 2006a; Valenzuela 2006b; Valenzuela 2009). Researchers investigating cognitive training in adults with subtle cognitive changes and MCI have concluded that it could

improve global cognitive function and increase performance on domain-specific outcome measures, with some studies also reporting reduced rates of incident dementia (Cheng 2012; Gates 2011a; Herrera 2012; Hoyer 2006; Unverzagt 2012; Zehnder 2009). Additionally, some clinical trial results indicate that computerised and online cognitive training in adults without dementia may improve daily functioning and psychological well-being (Gordon 2013; Kueider 2012; Rebok 2014; Zelinski 2009).

In this review, we focus on primary prevention, that is, the maintenance of cognitive function in cognitively healthy adults in late life (> 65 years of age) by means of computerised cognitive training (CCT). Companion reviews investigate the effects of CCT on cognitively healthy adults in midlife (40 to 65 years) and on people with MCI (Gates 2019a; Gates 2019b). We reviewed randomised controlled trials (RCTs) investigating the effects of CCT interventions over at least 12 weeks on cognitive performance, quality of life, and daily functioning. The inclusion criterion of an intervention duration of 12 or more weeks is consistent with cognitive training recommendations (Lampit 2015).

## How the intervention might work

Computerised programmes have been delivered in individual sessions and within groups, with supervision or privately at home, and there is wide variation in the 'dose' or length of each training session, the frequency of sessions, and the duration of training programmes, leading to significant heterogeneity in the literature (Gates 2014). However, the unifying theoretical premise behind cognitive training is that it will stimulate neuroplasticity, increase brain and cognitive reserve, and thereby maintain or improve cognitive function. It has also been suggested that cognitive stimulation may result in neural compensation, which is the development of compensatory networks maintaining cognitive performance, potentially masking or preventing clinical manifestation of neurocognitive disease (Grady 2012). Recently, to incorporate both the factors associated with age-related cognitive decline and those thought to enhance function and reserve, a scaffold theory of compensatory activation has been proposed (Park 2013). The interventions that fall within the scope of this review are not expected to modify dementia pathology, but it is hypothesised that the increase in mentally stimulating activity that these interventions induce will have an impact on the development of clinical dementia (Bennett 2014).

Although the evidence base is very limited, human trials of cognitive training suggest positive neuroplastic changes, including reduced  $\beta$ -amyloid burden (Landau 2012), as a result of the intervention. A number of diverse studies investigating neurophysiological changes using functional magnetic resonance imaging have identified increased prefrontal and parietal activity and hippocampal activation (Olesen 2004; Rosen 2011; Suo 2012a; Valenzuela 2003). Electroencephalography and magnetic resonance spectrometry studies of cognitive training support the con-

cept of functional neuroplasticity post training, with results indicating positive changes in brain metabolism, task-dependent brain activation, and resting-state networks (Belleville 2012; Berry 2010; Förster 2011). However, the research is limited, and significant further investigation is required.

## Why it is important to do this review

The prevalence and financial implications of dementia are such that small effects on cognitive decline, or on the incidence of dementia, may have a large impact on healthcare costs and the overall burden of dementia to society and to individuals with the disease. The potential of computerised cognitive-based interventions to be effective in improving cognitive health and function, along with their low implementation and administration costs and their high availability and accessibility, has led to the American Alzheimer's Association recommending development and testing of cognitive training as a research priority (Alzheimer's Association 2014).

To date, cognitive training research has been controversial, with insufficient data on which to base clear clinical guidelines for intervention. Results from meta-analyses have been inconsistent; negative findings have been reported, and opposing views have been published (Lampit 2015; Owen 2010; Papp 2009). Clinical trials have been criticised for poor specification of interventions, poor methodological rigour, small sample sizes, failure to assign treatments randomly, lack of active control, limited outcome measures to determine transfer of benefit to non-trained functions, and lack of longitudinal design to determine persistence of benefit (Gates 2010; Green 2014; Kueider 2012; Papp 2009; Park 2013; Reijnders 2013; Walton 2014). Additionally, results reported in some previous reviews have been hard to interpret, as cognitively healthy and clinical populations have been combined, and diverse types of cognitive intervention have been analysed together (e.g. Martin 2011). Recent meta-analyses in cognitively healthy older adults with defined intervention eligibility criteria have shown positive effects on cognition (Kueider 2012; Lampit 2014; Shao 2015). It is important to note that recent primary studies have identified that the benefits of CCT may depend upon a number of factors. Comparisons between single- and multiple-domain training suggest that multiple-domain training was better, consistent with increased global reserve (Cheng 2012), and nascent evidence suggests that different cognitive domains may respond differently to training, and hence may require different interventions for different durations (Lampit 2014).

For individuals, fear of cognitive decline and dementia may be a powerful motivator to seek preventive interventions. The World Alzheimer Report 2014 has reported that cognitively stimulating activities, including reading, playing musical instruments, and playing cards and board games, may be beneficial for improving, maintaining, and preventing decline in cognitive functioning, although most of these activities have not been investigated in clinical trials. Technology and computerised 'brain training' games

and cognitive training programmes are being investigated more actively (Alzheimer's Association 2014; Peretz 2011; Sixsmith 2013). However, the proliferation of computer-based commercial products purporting to improve cognitive function and reduce dementia risk has frequently outpaced thorough research into product benefits (Gates 2014; Lampit 2015). The value of the brain training industry has reportedly risen from \$295 million in 2009 to \$2 billion to \$8 billion in 2015 (www.sharpbrains.com). In this context, it is important to assist clinicians and consumers to make informed choices that are based on evidence, take account of alternative cognitively stimulating activities, and protect against strong advertising claims.

A robust review is therefore warranted to investigate the efficacy of computerised cognitive interventions and to evaluate potential sources of bias and heterogeneity in the literature. If sufficient trials are identified, then it is important to examine intervention characteristics and other factors that may affect outcomes, along with examining transfer and persistence of benefit. Information about adverse effects is also important, although behavioural interventions such as CCT are often perceived to be at 'low risk' for adverse effects (Gates 2014). The findings of this review should be useful for older adults, public health decision-making bodies, health practitioners, and researchers, providing them with a comprehensive synthesis of information about the current state of the evidence and identifying research gaps and unanswered questions in the field.

## OBJECTIVES

To evaluate the effects of computerised cognitive training interventions lasting at least 12 weeks for the maintenance or improvement of cognitive function in cognitively healthy people in late life.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included randomised controlled trials (RCTs) and quasi-RCTs, published or unpublished, reported in any language. Full reports and other types of reports, such as conference abstracts, were eligible for inclusion. We included studies involving both randomised and non-randomised trial arms, but we considered only results from the former. We included cross-over studies, but we extracted and analysed data from the first treatment period only.

## Types of participants

We included studies of cognitively healthy people in late life. 'Late life' was defined as over 65 years of age, in line with the World Health Organization (WHO) definition ([who.int/healthinfo/survey/ageingdefnolder/en/](http://who.int/healthinfo/survey/ageingdefnolder/en/)). At least 80% of the study population had to be in this age range. We covered healthy participants in midlife (40 to 65 years) in a separate review (Gates 2016a). If the age range of participants in a trial did not coincide with our categories, then we used the median and range, or the mean and standard deviation (SD), to place studies into the most appropriate review.

For a study to be included, its authors should have attempted to exclude those who were not cognitively healthy or who had dementia. We accepted and recorded the trial authors' own definitions of 'cognitively healthy'. It was acceptable, for this purpose, for authors to have used a cut-off score on a cognitive test as an exclusion criterion. We accepted any cut-offs used in the studies, and we examined this as a possible source of heterogeneity.

We excluded all studies where more than 20% of participants were reported to have subjective memory complaints, or to have received a diagnosis of any cognitive, neurological, psychiatric, or medical condition.

We contacted study authors if we needed further clarification to determine health status. If we received no response, clinical experts in our review group classified the trials, or listed them as 'Studies awaiting classification'.

## Types of interventions

We included studies of cognitive training interventions using interactive computerised technology of 12 or more weeks' duration compared with active or inactive control interventions.

Experimental interventions had to adhere to the following criteria: any form of interactive computerised cognitive intervention, including computer exercises, computer games, mobile devices, gaming console, and virtual reality, that involves repeated practice on standardised exercises of specified cognitive domain/s for the purpose of enhancing cognitive function.

By 'active control', we mean all those control conditions that involve unguided computer- and/or screen-based tasks that are not a planned intervention. These tasks can involve watching educational videos or playing computer games, with no particular training component. By 'inactive control', we refer to control groups in which no intervention is applied that may be expected to have an effect on cognition.

The minimum treatment duration was set at 12 weeks to evaluate the effects of training on meaningful long-term outcomes and to make a comment about the minimum 'dose' of training that may be required to effect an enduring change. Previous research suggests that acute brain changes can be seen following eight weeks of training (Engvig 2014); however, we are unable to find any evidence that such brain changes endure. Most studies examin-

ing the benefits of brain and cognitive reserve identify long-term cognitive stimulation from years of education. We therefore made an arbitrary judgement that at least 12 weeks of regular cognitive training would be required for an enduring effect of intervention. Additionally, this time frame is consistent with recommendations derived from reviews of clinical trials (Lampit 2014a).

There was no minimum duration of follow-up. However, all included trials had to report outcomes at a minimum of one time point - 12 or more weeks after randomisation. Trials in cognitively healthy people with a duration as short as 12 weeks typically investigate cognitive enhancement rather than maintenance of cognitive function. We included these trials to give a full picture of the data, although it is recognised that the relationship between short-term cognitive enhancement and maintenance of cognitive function over longer periods of time is unclear.

We excluded interventions that did not involve any form of computer delivery. We excluded studies where the experimental intervention was combined with any other form of intervention, unless the added intervention was provided in a standardised manner to both experimental and control groups.

## Types of outcome measures

### Primary outcomes

- Global cognitive functioning: measured using validated tests, for example (but not limited to):
  - Mini Mental State Examination (MMSE);
  - Alzheimer's Disease Assessment Scale (ADAS-Cog);
  - Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); and
  - Cambridge Cognition Examination (CAMCOG).

The main time point of interest was 'end of trial', defined as the time point with the longest follow-up duration, as measured from randomisation (see also section [Data collection and analysis](#)). We also extracted and presented outcome data reported at other time points after randomisation, where available.

### Secondary outcomes

Secondary outcomes are cognitive tests not included in the training programme, administered before and after training, that provide any validated measure of:

- specific cognitive functioning subdomain: episodic memory;
- specific cognitive functioning subdomain: speed of processing;
- specific cognitive functioning subdomain: executive function;
- specific cognitive functioning subdomain: attention/working memory;
- specific cognitive functioning subdomain: verbal fluency;

- quality of life/psychological well-being, either generic or health-specific;
- daily function, such as measures of instrumental activities of daily living; and
- number of participants experiencing one or more serious adverse event(s).

If a trial provided data on more than one cognitive scale for a specific outcome, we applied a hierarchy of cognition-related outcomes (manuscript in preparation) and used data on the cognitive scale that was highest in this hierarchy. For example, if a trial reported results on both the Mini Mental State Examination and the Clinical Dementia Rating scale (CDR), we used outcome data from the MMSE in our quantitative analyses. The order of a scale in the hierarchy was determined by the frequency of its use in a large set of 79 trials, evaluating vitamin and mineral supplementation, dietary interventions, and physical exercise interventions.

### Outcomes to be included in the 'Summary of findings' table

We planned to address critical effectiveness outcomes in the 'Summary of findings' table for each review. We included all outcomes related to cognitive function on non-trained tasks and quality of life. We were able to include for the first comparison the following outcomes: (1) global cognitive functioning, (2) episodic memory, (3) speed of processing, (4) executive functioning, (5) working memory, (6) quality of life, (7) adverse events. For the second comparison, we included the following outcomes: (1) episodic memory, (2) speed of processing, (3) executive functioning, (4) working memory, and (5) verbal fluency.

## Search methods for identification of studies

### Electronic searches

We searched ALOIS ( [www.medicine.ox.ac.uk/alois](http://www.medicine.ox.ac.uk/alois)) - the specialised register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG) - up to 31 March 2018. ALOIS was maintained by the Information Specialist for the CDCIG and contains studies that fall within the areas of dementia prevention, dementia treatment and management, and cognitive enhancement in healthy elderly populations. These studies are identified through:

- monthly searches of several major healthcare databases: MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, and Latin American Caribbean Health Sciences Literature (LILACS);
- monthly searches of several trial registers: University hospital Medical Information Network ( UMIN) Clinical Trials Registry ( Japan) ( UMIN-CTR) ( [www.umin.ac.jp/ctr/index.htm](http://www.umin.ac.jp/ctr/index.htm)); World Health Organization ( WHO) portal ( which covers ClinicalTrials.gov ( [clinicaltrials.gov/](http://clinicaltrials.gov/)); International

Standard Randomized Controlled Trials Number ( ISRCTN) ( [www.isrctn.com/](http://www.isrctn.com/)); Chinese Clinical Trials Register ( ChiCTR) ( [who.int/ictrp/network/chictr/en/](http://who.int/ictrp/network/chictr/en/)); German Clinical Trials Register ( GermanCTR) ( [who.int/ictrp/network/drks2/en/](http://who.int/ictrp/network/drks2/en/)); Iranian Registry of Clinical Trials ( IRCT) ( [who.int/ictrp/network/irct2/en/](http://who.int/ictrp/network/irct2/en/)); and The Netherlands National Trials Register ( NTR) ( [who.int/ictrp/network/ntr/en/](http://who.int/ictrp/network/ntr/en/)), plus others);

- quarterly searches of the Central Register of Controlled Trials of the Cochrane Library (CENTRAL); and
- six-monthly searches of several grey literature sources: Institute for Scientific Information (ISI) Web of Knowledge Conference Proceedings; Index to Theses; and Australasian Digital Theses.

To view a list of all sources searched for ALOIS, see [About ALOIS](#), on the ALOIS website ( [www.medicine.ox.ac.uk/alois](http://www.medicine.ox.ac.uk/alois)).

Details of the search strategies run in healthcare bibliographic databases, used for retrieval of reports of dementia, cognitive improvement, and cognitive enhancement trials, can be viewed in the 'Methods used in reviews' section within the editorial information about the Cochrane [Dementia and Cognitive Improvement Group](#).

We conducted additional searches in MEDLINE, Embase, PsycINFO, CINAHL, CENTRAL, ClinicalTrials.gov, and the WHO Portal/ICTRP ( [www.apps.who.int/trialsearch](http://www.apps.who.int/trialsearch)) to ensure that the searches were as comprehensive and as up-to-date as possible, in identifying published, unpublished, and ongoing trials. The search strategies used are shown in [Appendix 1](#).

### Searching other resources

We screened the reference lists of all included trials. In addition, we screened the reference lists of recent systematic reviews, health technology assessment reports, and subject-specific guidelines identified through [www.guideline.gov](http://www.guideline.gov). We restricted the search to those guidelines meeting National Guideline Clearinghouse (NGC) 2013 published inclusion criteria.

We contacted experts in the field and companies marketing included interventions to request additional randomised trial reports not identified by the search.

### Data collection and analysis

We used this protocol alongside instructions for data extraction, quality assessment, and statistical analyses generated by the editorial board of CDCIG, and based in part on a generic protocol approved by the Cochrane Musculoskeletal Group for another series of reviews (da Costa 2012; da Costa 2014; Reichenbach 2010; Rutjes 2009a; Rutjes 2009b; Rutjes 2010).

## Selection of studies

If multiple reports described the same trial, we included all of them to allow extraction of complete trial details.

We used crowdsourcing to screen the search results. Details of this are available at [www.medicine.ox.ac.uk/alois/content/modifiable-risk-factors](http://www.medicine.ox.ac.uk/alois/content/modifiable-risk-factors). In brief, teams of volunteers would perform a 'first assess' on the search results. The crowd was recruited through the network called Students For Best Evidence ([www.students4bestevidence.net](http://www.students4bestevidence.net)). The crowd provided an initial screen of search results using an online tool developed for the Cochrane Embase project, but tailored for this programme of work. The crowd decided (based on reading of title and abstract) whether the citation is describing a randomised or quasi-randomised trial, irrespective of the citation topic. It is estimated that this approach removes 75% to 90% of results retrieved. We then screened the remaining results (titles and abstracts). Four independent review authors (NG, EM, SK, RV) assessed the full text of studies for eligibility, with any disagreements resolved by a fifth independent review author.

We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and [Characteristics of excluded studies table](#) (Moher 2009). We did not impose any language restrictions.

## Data extraction and management

Five review authors (NG, MN, SK, RV, GM), working independently, extracted trial information using a standardised and piloted extraction method, while referring also to a guidance document and resolving discrepancies by discussion or by involvement of a fifth review author. Where possible, we extracted the following information related to characteristics of participants, interventions, and study design.

### Participant characteristics

- Gender
- Age (range, median, mean)
- Education (level and years of education)
- Baseline cognitive function
- Cognitive diagnostic status
- Duration of cognitive symptoms
- Ethnicity
- Apo-E genotype
- Vascular risk factors (hypertension, diabetes, hyperlipidaemia)
- Body mass index (BMI)
- Depression and stress
- Physical activity
- Work status

### Intervention characteristics

- Type and description of computerised cognition-based intervention
- Type and description of the control condition
- Delivery mode (individualised, group sessions, supervised)
- Length of training sessions (in minutes)
- Frequency of sessions (per week)
- Duration of treatment programme
- Any concomitant treatments where benefits can be isolated from the intervention

### Methodological characteristics

- Trial design (individual or cluster randomisation, parallel-group, factorial, or cross-over design)
- Number of participants
- Allocation to trial (randomisation, blind allocation)
- Outcome measures used
- Duration of follow-up (as measured from randomisation)
- Duration of follow-up (as measured from end of treatment)
- Source of financial support
- Publication status

If outcome data were available at multiple time points within a given trial, we extracted data at 12 weeks, as well as short-term (up to one year), medium-term (one to two years), and long-term results (more than two years). Within these time periods, we extracted the latest data reported by the study (e.g. if the study reported data at six months, nine months, and one year, we extracted only the one-year data and analysed these for the one-year (short-term) time point). For dichotomous outcomes (such as number of participants experiencing one or more serious adverse events), we extracted from each trial the number of participants with each outcome, at each time point. For continuous outcomes, we extracted the number of participants for whom the outcome was measured, and determined the mean and SD of the change from baseline for each outcome at each time point. If changes from baseline data were not available, we extracted the mean value at each time point. When necessary and possible, we approximated means and measures of dispersion from figures in the reports. For cross-over trials, we extracted data on the first treatment period only. Whenever possible, we extracted intention-to-treat data (i.e. analysing all participants according to the group randomisation); if this information was not available, we extracted and reported data from available case analyses. If none of these data were available, we considered data from per-protocol analyses. We contacted trial authors if we could not obtain the necessary data from the trial report.

### Assessment of risk of bias in included studies

After completion of a standardised training session (provided by AR), one member of the review author team and one experienced review author provided by the editorial team independently assessed the risk of bias in each of the included trials, using



Cochrane's 'Risk of bias' tool (Higgins 2011), and resolving disagreements by consensus. We assessed the risk of bias potentially introduced by suboptimal design choices with respect to sequence generation, concealment of allocation, blinding of participants and caregivers, blinded outcome assessment, selective outcome reporting, and incomplete outcome data, including the type of statistical analysis used (true intention-to-treat vs other). Based on the aforementioned criteria, we rated studies as having 'low risk', 'unclear risk', or 'high risk' of bias for each domain, including a description of the reasoning for our rating. The general definitions used are provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We derived review-specific definitions in part from a previously published systematic review (Rutjes 2012), and we explained them in detail in Appendix 2.

### Measures of treatment effect

The measure of treatment effect for continuous outcomes was effect size (standardised mean difference), defined as the between-group difference in mean values divided by the pooled SD. In case a single trial contributed to a comparison, or if all studies used the same instrument, we used the mean difference to describe and analyse results. We expressed the treatment effect for dichotomous outcomes as a risk ratio (RR) with a 95% confidence interval (CI).

### Unit of analysis issues

We identified no cluster-randomised or cross-over trials for inclusion.

### Dealing with missing data

Missing data in individual trials may put study estimates of effects at high risk of bias and may lower the overall quality of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group ([www.gradeworkinggroup.org](http://www.gradeworkinggroup.org)). We dealt with missing data in our 'Risk of bias' assessments and evaluated attrition bias in stratified analyses of the primary outcomes (Appendix 2). We analysed available information and did not contact study authors with requests to provide missing information, nor did we impute missing data ourselves.

### Assessment of heterogeneity

We planned to examine heterogeneity in stratified analyses by trial, participant, and intervention. We also planned to visually inspect forest plots for the presence of heterogeneity and to calculate the variance estimate  $\tau^2$  as a measure of between-trial heterogeneity (DerSimonian 1986). We prespecified a  $\tau^2$  of 0.04 to represent low heterogeneity, 0.09 to represent moderate heterogeneity, and 0.16 to represent high heterogeneity between trials (Spiegelhalter 2004). In addition, we used the  $I^2$  statistic and the corresponding  $\chi^2$  test to assist readers more familiar with these statistics

(Higgins 2011).  $I^2$  describes the percentage of variation across trials attributable to heterogeneity rather than to chance, with values of 25%, 50%, and 75% interpreted as low, moderate, and high (respectively) between-trial heterogeneity. We preferred  $\tau^2$  over  $I^2$  in interpretation of between-trial heterogeneity, as interpretation of  $I^2$  can be largely affected by the precision of trials included in the meta-analysis (Rücker 2008). All P values are two-sided.

### Assessment of reporting biases

We did not identify a sufficient number of trials to formally explore reporting biases and other biases related to small-study effects (see [Differences between protocol and review](#)).

### Data synthesis

We reported summary and descriptive statistics (means and SDs) for participant and intervention characteristics. Additionally, we used standard inverse-variance random-effects meta-analysis to combine outcome data across trials at end of trial (DerSimonian 1986), and, if possible, at least one additional time point (see [Primary outcomes](#) and [Data collection and analysis](#) for definitions of time points). We conducted statistical analyses in Review Manager 5 (RevMan 2014), as well as in STATA, release 13 (Statacorp, College Station, Texas, USA).

### GRADE and 'Summary of findings' table

We used GRADE to describe the quality of the overall body of evidence for each outcome in the 'Summary of findings' table (Guyatt 2008; Higgins 2011). We defined 'quality' as the degree of confidence that we can place in the estimates of treatment benefits and harms. Four ratings were possible: high, moderate, low, and very low. Rating evidence as 'high quality' implies that we are confident in our estimate of the effect, and further research is very unlikely to change this. A rating of 'very low' quality implies that we are very uncertain about the obtained summary estimate of effect. The GRADE approach rates evidence from RCTs that do not have serious limitations as 'high quality'. However, several factors can lead to downgrading of evidence to 'moderate', 'low', or 'very low'. The degree of downgrading is determined by the seriousness of these factors: study limitations (risk of bias); inconsistency; indirectness of evidence; imprecision; and publication bias (Guyatt 2008; Higgins 2011).

### Subgroup analysis and investigation of heterogeneity

Due to the limited number of trials identified, we were unable to conduct protocol-defined subgroup and sensitivity analyses (see [Differences between protocol and review](#)).

## RESULTS

## Description of studies

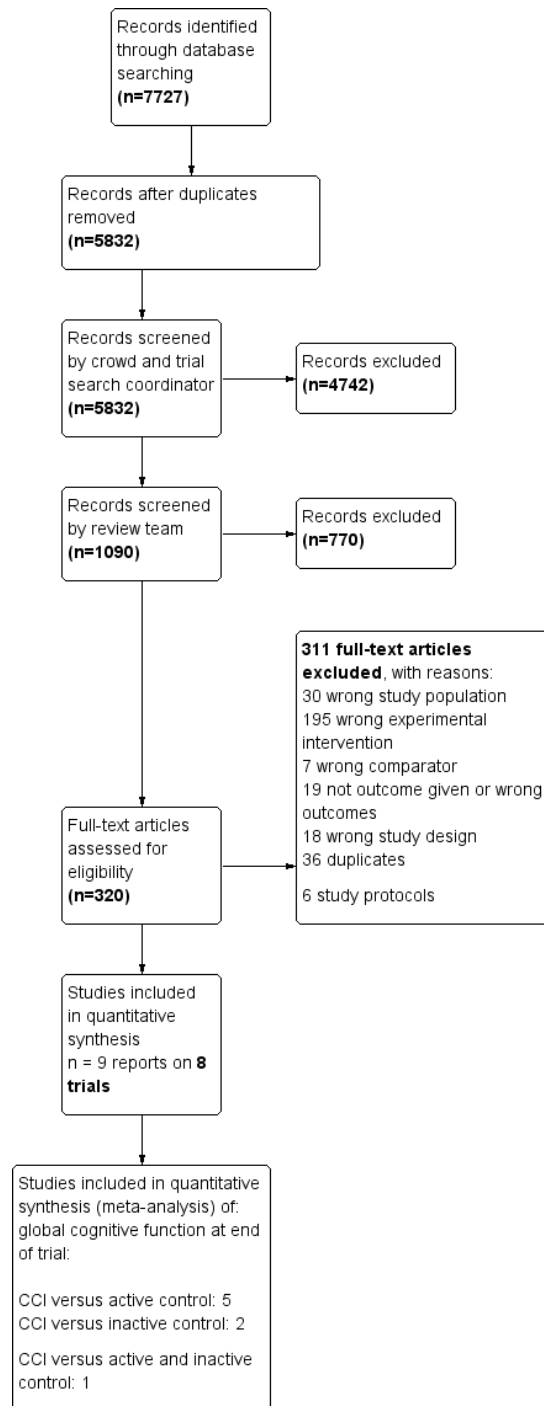
See [Characteristics of included studies](#), [Characteristics of excluded studies](#), [Characteristics of studies awaiting classification](#), and [Characteristics of ongoing studies](#).

## Results of the search

We conducted searches in January 2015, July 2015, February 2016, July 2016, and March 2018. In total, we retrieved 7727 records from the five searches. After de-duplication, 5832 re-

mained. A crowd (through crowdsourcing) and the CDCIG Information Specialist assessed these at title and abstract level. In total, 1090 results remained after this assessment. The review team then assessed these records. Of these, we assessed 320 full-text articles for eligibility and found that eight studies (reported in nine articles) were eligible for inclusion ([Desjardins-Crépeau 2016](#); [Klusmann 2010](#); [Lampit 2014](#); [Legault 2011](#); [Leung 2015](#); [Peretz 2011](#); [Shatil 2013](#); [van het Reve 2014](#)). This process is depicted in [Figure 1](#).

**Figure 1. Study flow diagram.**





## Included studies

We have provided details of the eight eligible studies in the [Characteristics of included studies](#) tables and have briefly summarised them below.

### Design

All studies used a randomised controlled design. Three used a factorial  $2 \times 2$  design ([Desjardins-Crépeau 2016](#); [Legault 2011](#); [Peretz 2011](#)), and the remainder used a parallel design. Durations of the included studies were 12 weeks ([Desjardins-Crépeau 2016](#); [Leung 2015](#); [Peretz 2011](#); [van het Reve 2014](#)), four months ([Legault 2011](#); [Shatil 2013](#)), seven months ([Klusmann 2010](#)), and 15 months ([Lampit 2014](#)).

### Sample size

[Desjardins-Crépeau 2016](#) included 136 participants in total and reported data on 42 participants in the experimental group and 34 in the control group. [Klusmann 2010](#) included 92 participants in the experimental group and 76 in the control group. [Lampit 2014](#) randomised 41 people to the experimental group and 39 to the control group. [Legault 2011](#) randomised 18 participants to cognitive training, 19 to the combined intervention (cognitive training and exercise), and 18 to control. [Leung 2015](#) included 109 participants in the experimental group and 100 in the control group. [Peretz 2011](#) randomised 84 participants to the experimental group and 71 to the control group. [Shatil 2013](#) randomised 42 to 48 participants in each of the four arms of the study (total 180 participants). Finally, [van het Reve 2014](#) randomised 84 participants to the intervention group and 98 to the control group.

### Setting

[Desjardins-Crépeau 2016](#) did not provide information regarding the setting. [Klusmann 2010](#) undertook this investigation in Germany but provided few details about the setting. [Lampit 2014](#), [Leung 2015](#), and [Peretz 2011](#) were single-centre studies conducted in Australia, Hong Kong, and Israel, respectively. [Legault 2011](#) and [Shatil 2013](#) were single-centre studies conducted in the USA. Fourteen centres from Switzerland and Germany participated in [van het Reve 2014](#).

### Participants

All participants were cognitively healthy with a minimum age of 65 years or older, other than those in [Desjardins-Crépeau 2016](#), who were 60 years or older (the mean age in all groups in this study was > 70 years; therefore we considered that inclusion in this review was

warranted). Mean ages ranged from 67 to 82 years. Most studies except [Legault 2011](#) reported a preponderance of women. None of the studies focused on high-risk groups for cognitive decline.

## Interventions

### CCT versus active control

[Desjardins-Crépeau 2016](#) compared computerised dual task cognitive exercises versus an active control (lessons to introduce participants to computers and diverse software, e.g. Word, Excel, and an introduction to the Internet, e.g. search engines, websites, on-line games). Researchers randomised participants in both groups to receive either aerobic and resistance exercises or stretching and toning exercises in a  $2 \times 2$  factorial design. [Lampit 2014](#) compared computerised COGPACK cognitive training exercises targeting five cognitive domains (memory, attention, response speed, executive functions, and language) versus an active control condition of watching educational videos and answering multiple choice questions. Similarly, [Leung 2015](#) compared computerised cognitive training exercises versus an active control of watching educational videos (e.g. history, science) followed by questions. [Peretz 2011](#) compared the CogniFit Personal Coach programme versus an active control of traditional computer games. [Legault 2011](#) compared a computerised memory domain training programme in small groups monitored by skilled trainers versus an active control of weekly health lectures provided by an instructor and promotion of group interaction.

### CCT versus inactive control

[Klusmann 2010](#) compared a computer course that included multiple computer activities such as creative, co-ordinative, and memory tasks versus an inactive, no intervention control. [van het Reve 2014](#) compared a strength-balance-cognitive programme - the CogniPlus computerised cognitive training programme - versus a strength-balance programme.

### CCT versus both active and inactive controls

We included [Shatil 2013](#) in our comparisons of computerised training versus both active and inactive controls. This study included four arms: (1) Cognifit, (2) Cognifit in combination with group-based supervised physical training, (3) supervised physical training, and (4) active control of book club reading. Therefore, we included [Shatil 2013](#) in comparisons of computerised cognitive training (Cognifit) plus physical training versus physical training as inactive control, and computerised cognitive training (Cognifit) versus book club reading as active control.

## Outcomes

In this section, we describe outcome measures that we included in meta-analyses in this review (see [Types of outcome measures](#)). We describe instruments that address outcomes of interest to this review but that were not included in any meta-analyses in the [Characteristics of included studies](#) tables.

## Primary outcome

### *Global cognitive function*

[Lampit 2014](#) measured global cognitive functioning using a composite score of memory, speed, and executive function after 3 and 15 months of follow-up. [Peretz 2011](#) measured global cognitive functioning using an overall NexAde battery test composite score at three months.

## Secondary outcomes

### *Cognitive function subdomain: episodic memory*

Episodic memory was measured with the Rey Auditory Verbal Learning Test (RAVLT) by [Desjardins-Cr peau 2016](#), the Rivermead Behavioural Memory Test (RBMT) by [Klusmann 2010](#), the Logical Memory subtest of the Wechsler Memory Scale-III (WMS-III) by [Legault 2011](#) and [Leung 2015](#), and a memory recall test from the NexAde cognitive test battery by [Peretz 2011](#).

### *Cognitive function subdomain: speed of processing*

[Shatil 2013](#) used the CogniFit neuropsychological evaluation subtest speed of visual information processing (SVP) to measure speed of processing. [Desjardins-Cr peau 2016](#) and [van het Reve 2014](#) used the Trail Making Test (TMT)-A, to measure speed of processing.

### *Cognitive function subdomain: executive function*

[Legault 2011](#) used TMT-B and -A, and [van het Reve 2014](#) used TMT-B, to measure executive function. [Klusmann 2010](#) assessed executive function with the Stroop test, [Peretz 2011](#) used the Executive functions subtest of NexAde, and [Desjardins-Cr peau 2016](#) used the Color-Word Interference Test (CWIT) of the Delis-Kaplan Executive Functions System (CWIT-switching).

### *Cognitive function subdomain: working memory*

Working memory was measured with the Digit Span by [Leung 2015](#), the NexAde Visuospatial working memory subtest by [Peretz 2011](#), and the auditory working memory (AM) subtest of CogniFit by [Shatil 2013](#).

### *Cognitive function subdomain: verbal fluency*

Verbal fluency was measured via semantic verbal fluency by [Klusmann 2010](#).

### *Quality of life/psychological well-being*

None of the included studies reported on these outcomes.

### *Daily functioning*

None of the included studies reported on this outcome.

### *Number of participants experiencing one or more serious adverse events*

None of the studies reported on this outcome.

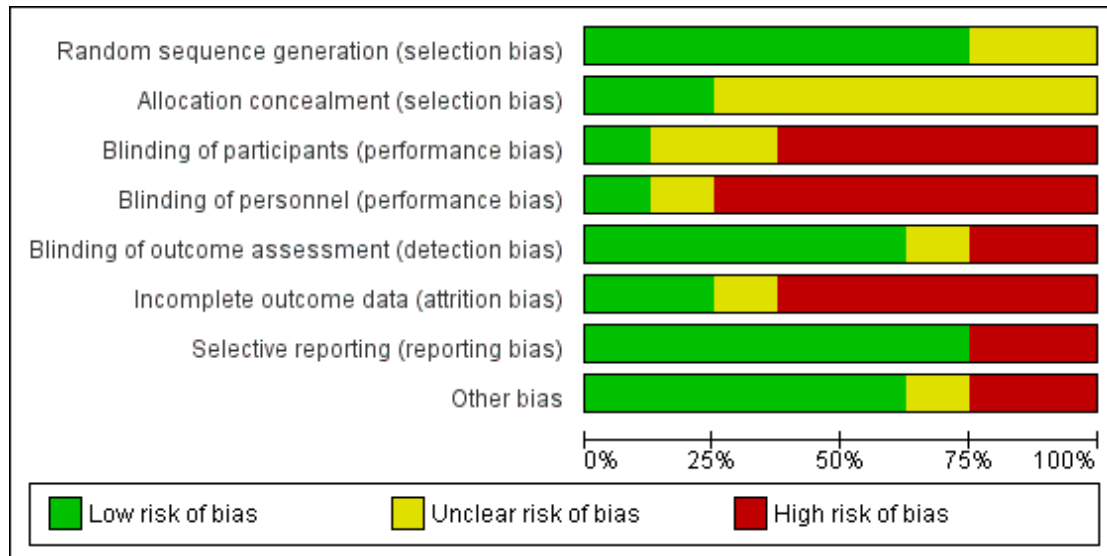
## Excluded studies

We excluded 311 full-text articles that we had examined in full text. Of these, we excluded one because it focused on cognitively healthy people in midlife ([Corbett 2015](#)), another because the age of participants was given as ranging from 50 to 85 without means and standard deviations ([Shah 2012](#)), and eight because participants had mild cognitive impairment ([Barnes 2013](#); [Djabelkhir 2017](#); [Fiatarone Singh 2014](#); [Gooding 2016](#); [Herrera 2012](#); [Kwok 2013a](#); [Optale 2010](#); [Rozzini 2007](#)). Nine of these trials are included in two other Cochrane reviews ([Gates 2019a](#); [Gates 2019b](#)). We excluded 195 studies because they investigated an intervention shorter than 12 weeks, or because the intervention did not involve computerised cognitive training, and 18 studies because they used the wrong study design. We did not identify any ongoing trials in trial registers or conference proceedings. Reasons for study exclusion can be found in [Characteristics of excluded studies](#).

## Risk of bias in included studies

For graphical presentation of the risk of bias assessments, please see [Figure 2](#) and [Figure 3](#).

**Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**



**Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants (performance bias)	Blinding of personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Desjardins-Crépeau 2016	+	?	-	-	+	-	+	+
Klusmann 2010	+	?	-	-	+	-	+	+
Lampit 2014	+	+	+	-	+	+	-	+
Legault 2011	?	?	-	-	+	+	-	-
Leung 2015	+	?	-	-	-	?	+	?
Peretz 2011	+	+	-	+	+	-	+	+
Shatil 2013	?	?	?	?	?	-	+	-
van het Reve 2014	+	?	?	-	-	-	+	+

## Allocation

We considered there to be low risk of selection bias for two studies, which reported adequate methods to generate random sequences and conceal allocation ([Lampit 2014](#); [Peretz 2011](#)). For three trials, we considered that there was an adequate method of random sequence generation but little or no information about allocation concealment; we therefore judged them to be at unclear risk ([Klusmann 2010](#); [Leung 2015](#); [van het Reve 2014](#)). In the remaining two trials, the risk of bias associated with both sequence generation and concealment of allocation was unclear ([Legault 2011](#); [Shatil 2013](#)).

## Blinding

We considered there to be an unclear risk of performance and detection bias for one study, which lacked information on blinding of participants, personnel, and outcome assessors ([Shatil 2013](#)). We considered two studies to be at high risk of performance bias because patients and personnel were not blinded to the treatment assigned, but at low risk of detection bias because blinding of outcome assessors was described ([Klusmann 2010](#); [Legault 2011](#)). [Lampit 2014](#) described adequate blinding of participants and outcome assessors, but not of personnel, so we considered it to be at high risk of performance bias and low risk of detection bias. We considered [Leung 2015](#) to be at high risk of both performance and detection bias because patients, personnel, and outcome assessors were not blinded. [Peretz 2011](#) described blinding of personnel and outcome assessors, but not of participants, so we considered it to be at high risk of performance bias and low risk of detection bias. [van het Reve 2014](#) did not report any details regarding blinding of participants but had high risk of both performance and detection bias because neither the personnel nor the outcome assessors were blinded.

## Incomplete outcome data

We considered two studies to be at low risk of attrition bias ([Lampit 2014](#); [Legault 2011](#)), and we judged one study to be at unclear risk because of lack of information about how missing data were handled ([Leung 2015](#)). We considered [Klusmann 2010](#), [Desjardins-Cr peau 2016](#), and [Shatil 2013](#) to be at high risk of attrition bias because on average less than 90% of the randomised participants were analysed. The authors of [Peretz 2011](#) stated that they used an intention-to-treat (ITT) analysis, but 18 participants in the experimental group and 16 in the control group did not complete the training and had no data available at baseline, follow-up, or both; we considered this to present high risk of attrition bias. We considered [van het Reve 2014](#) to have high risk of attrition

bias because only 82% and 78% of participants randomised to the two treatment groups were included in the statistical analyses.

## Selective reporting

We considered five studies to be at low risk of reporting bias because all outcomes are described in the results section of the articles ([Klusmann 2010](#); [Leung 2015](#); [Peretz 2011](#); [Shatil 2013](#); [van het Reve 2014](#)). We considered two studies to be at high risk of reporting bias because we identified differences between the trial registry entry and the final article ([Lampit 2014](#); [Legault 2011](#)).

## Other potential sources of bias

We assessed [Legault 2011](#) to be at high risk of bias for other reasons because the attendance rate in the combined CCT and physical activity group was statistically significantly better than in the physical activity only control group ([Legault 2011](#)). We assessed [Shatil 2013](#) to be at high risk of bias for other reasons because Shatil works for the CogniFit company.

## Effects of interventions

See: [Summary of findings for the main comparison](#); [Summary of findings 2](#)

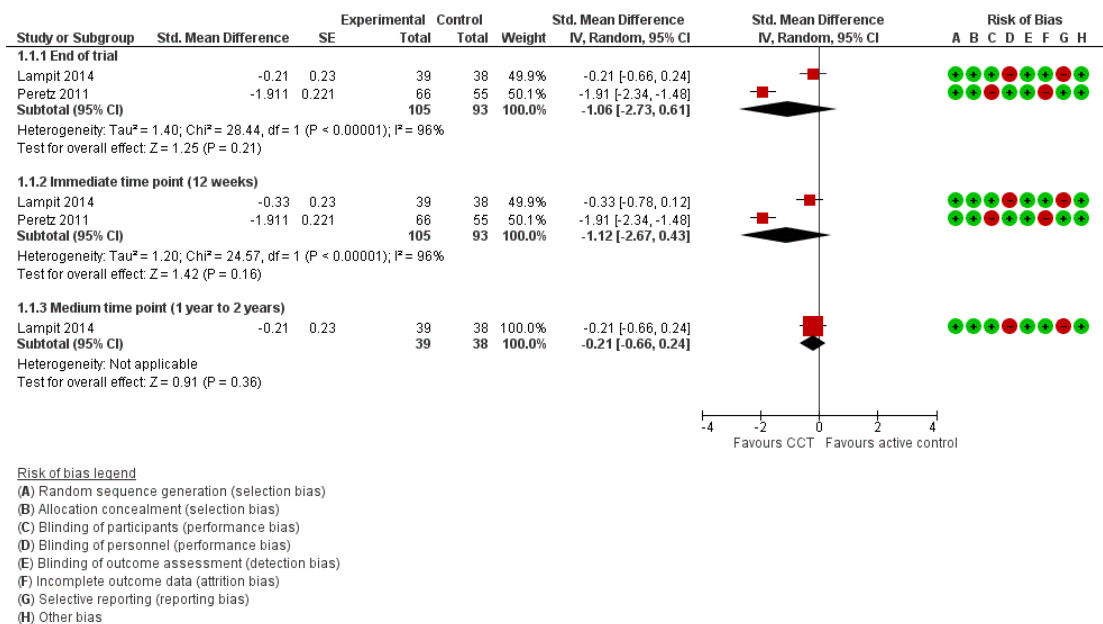
## Comparison: computerised cognitive training versus active control

We refer to [Summary of findings for the main comparison](#) for an overview related to the comparison computerised cognitive training (CCT) versus active control. Unless otherwise stated, all outcomes were independent neuropsychological measures, not trained tasks, and any change would suggest transfer of training effects.

## Primary outcome

Evidence on global cognitive function at end of trial was of very low quality, downgraded for imprecision, inconsistency, and risk of bias ([Analysis 1.1](#); [Figure 4](#)). Therefore we are very uncertain of this result. Negative values favour the CCT group. Two studies contributed to the analysis at end of trial ([Lampit 2014](#); [Peretz 2011](#)), yielding an SMD of -1.06 (95% CI -2.73 to 0.61; 2 studies; 198 participants). Results at individual time points are as follows: immediate time point (12 weeks) SMD -1.12 (95% CI -2.67 to 0.43; 2 studies; 198 participants) and medium time point (one to two years) SMD -0.21 (95% CI -0.66 to 0.24; 1 study; 77 participants). Results at both time points were imprecise and consistent, with effects in either direction.

**Figure 4. Forest plot of comparison: I Computerised cognition-based training versus active control, outcome: I.I Global cognitive function.**

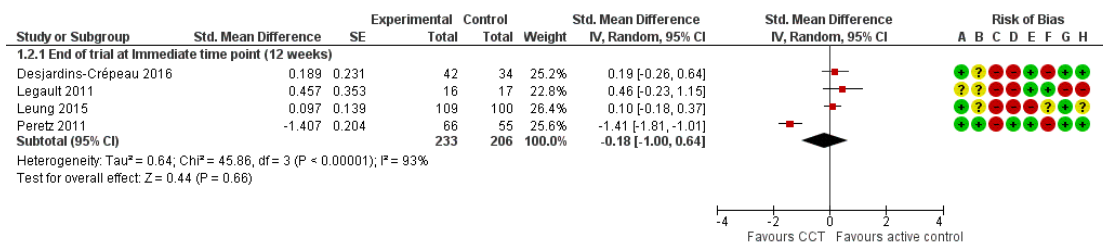


## Secondary outcomes

### Cognitive subdomain: episodic memory

Evidence on episodic memory at end of trial was of very low quality, downgraded for imprecision, inconsistency, and risk of bias (Analysis 1.2; Figure 5). Therefore we are very uncertain of this result. Negative values favour the CCT group. Four studies contributed to the analysis at end of trial, for 12 weeks in all cases (Desjardins-Cr peau 2016; Legault 2011; Leung 2015; Peretz 2011), yielding an SMD of -0.18 (95% CI -1.00 to 0.64; 4 studies; 439 participants).

**Figure 5. Forest plot of comparison: I Computerised cognition-based training versus active control, outcome: I.2 Episodic memory.**



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants (performance bias)
- (D) Blinding of personnel (performance bias)
- (E) Blinding of outcome assessment (detection bias)
- (F) Incomplete outcome data (attrition bias)
- (G) Selective reporting (reporting bias)
- (H) Other bias

### Cognitive subdomain: speed of processing

Two studies provided very low-quality evidence on speed of processing at end of trial (12 weeks) (Analysis 1.3) (Desjardins-Crépeau 2016; Shatil 2013). We downgraded the evidence for imprecision, inconsistency, and risk of bias. Therefore we are very uncertain of this result. Negative values favour the CCT group. The SMD was -0.63 (95% CI -1.14 to -0.12; 2 studies; 138 participants).

### Cognitive subdomain: executive function

Evidence on executive function at end of trial was of very low quality, downgraded for imprecision, inconsistency, and risk of bias (Analysis 1.4). Therefore we are very uncertain of this result. Negative values favour the CCT group. Included studies were Desjardins-Crépeau 2016, Legault 2011, and Peretz 2011, and end of trial in all cases was 12 weeks. The SMD was -0.34 (95% CI -1.45 to 0.77; 3 studies; 230 participants).

### Cognitive subdomain: working memory

Evidence on working memory at end of trial was of very low quality (Analysis 1.5), downgraded for imprecision, inconsistency, and risk of bias. Therefore we are very uncertain of this result. Negative values favour the CCT group. Three studies contributed to the analysis at end of trial (12 weeks) (Leung 2015; Peretz 2011;

Shatil 2013), yielding an SMD of -1.01 (95% CI -2.54 to 0.53; 3 studies; 392 participants).

### Comparison: computerised cognitive training versus inactive control

We refer to Summary of findings 2 for an overview related to the comparison CCT versus inactive control. Unless otherwise stated, all outcomes were independent neuropsychological measures, not trained tasks, and any change would suggest transfer of training effects.

#### Primary outcome

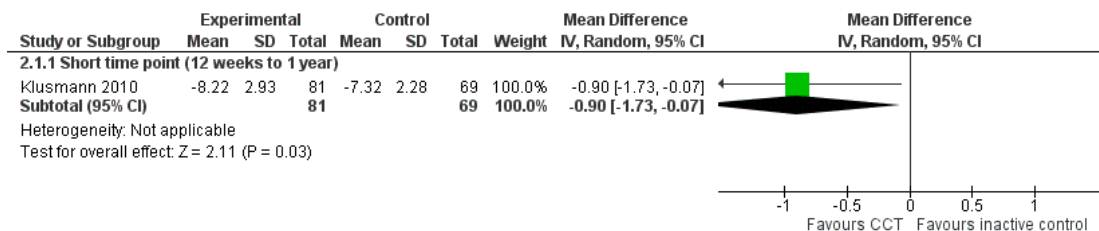
No studies provided data on global cognitive function at end of trial.

#### Secondary outcomes

#### Cognitive subdomain: episodic memory

Evidence on episodic memory at end of trial was of low quality, downgraded for imprecision and risk of bias (Analysis 2.1; Figure 6). Negative values favour the CCT group. The analysis (> 12 weeks to one year) included one study and yielded an MD of -0.90 (95% CI -1.73 to -0.07; 150 participants) (Klusmann 2010).

**Figure 6. Forest plot of comparison: 2 Computerised cognition-based training versus inactive control, outcome: 2.1 Episodic memory.**



### Cognitive subdomain: speed of processing

Two studies provided very low-quality evidence on speed of processing at end of trial (12 weeks) ([Analysis 2.2](#)) ([Shatil 2013](#); [van het Reve 2014](#)). We downgraded the evidence for imprecision, inconsistency, and risk of bias. Therefore we are very uncertain of this result. Negative values favour CCT. The SMD was -0.28 (95% CI -0.82 to 0.26; 2 studies; 204 participants).

### Cognitive subdomain: executive function

Evidence on executive function at end of trial was of low quality, downgraded for imprecision and risk of bias ([Analysis 2.3](#)). Negative values favour the CCT group. The analysis included two studies and yielded an SMD of -0.08 (95% CI -0.31 to 0.15; 2 studies; 292 participants) ([Klusmann 2010](#); [van het Reve 2014](#)). Results at individual time points were as follows: 12 weeks SMD -0.03 (95% CI -0.35 to 0.30; 1 study; 144 participants) and short-term follow-up (> 12 weeks to one year) SMD -0.13 (95% CI -0.45 to 0.20; 1 study; 148 participants).

### Cognitive subdomain: working memory

One study provided low-quality evidence on working memory at end of trial ([Analysis 2.4](#)) ([Shatil 2013](#)). We downgraded the evidence because of imprecision and risk of bias. Negative values favour CCT. At end of trial (12 weeks), the MD was -0.08 (95% CI -0.43 to 0.27; 1 study; 60 participants). This result means that, when compared with an inactive control, there may be little or no effect of CCT on working memory.

### Cognitive subdomain: verbal fluency

One study provided low-quality evidence on verbal fluency at end of trial ([Analysis 2.5](#)) ([Klusmann 2010](#)). We downgraded the evidence for imprecision and risk of bias. Negative values favour CCT. At end of trial (> 12 weeks to one year), the MD was -0.11 (95% CI -1.58 to 1.36; 1 study; 150 participants). This result means that, when compared with an inactive control, there may be little or no effect of CCT on verbal fluency.

### Subgroup analyses and sensitivity analyses

We could perform no subgroup analyses as too few studies contributed to the meta-analyses (see [Differences between protocol and review](#)).



## ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Computerised cognitive training compared with inactive control in cognitively healthy people in late life				
<b>Patient or population:</b> cognitively healthy people in late life <b>Settings:</b> general population <b>Intervention:</b> computerised cognitive training <b>Comparison:</b> inactive control intervention				
Outcomes	Difference between CCT and control (95% CI)*	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Global cognitive function measured at the end of follow-up	Not reported using a validated measure			
Cognitive subdomain: episodic memory measured at the end of follow-up	MD 0.90 lower (1.73 lower to 0.07 lower)	150 participants (1 study)	⊕⊕○○ <b>low<sup>b</sup></b>	CCT may improve slightly episodic memory when compared to inactive control
Cognitive subdomain: speed of processing measured at the end of follow-up	SMD 0.28 lower (0.82 lower to 0.26 higher)	204 participants (2 studies)	⊕○○○ <b>very low<sup>c</sup></b>	It is uncertain whether CCT maintains speed of processing better than inactive control
Cognitive subdomain: executive functioning measured at the end of follow-up	SMD 0.08 lower (0.31 lower to 0.15 higher)	292 participants (2 studies)	⊕⊕○○ <b>low<sup>b</sup></b>	CCT may lead to little or no improvement in executive functioning when compared to inactive control
Cognitive subdomain: working memory measured at the end of follow-up	MD 0.08 lower (0.43 lower to 0.27 higher)	60 participants (1 study)	⊕⊕○○ <b>low<sup>b</sup></b>	CCT may lead to little or no improvement in working memory when compared to inactive control
Cognitive subdomain: verbal fluency measured at the end of follow-up	MD 0.11 lower (1.58 lower to 1.36 higher)	150 participants (1 study)	⊕⊕○○ <b>low<sup>b</sup></b>	CCT may lead to little or no improvement in verbal fluency when compared to inactive control
Quality of life	Not reported using a validated measure			

Number of participants experiencing 1 or more serious adverse events	Not reported using a validated measure
<p>* The <b>risk in the intervention group</b> (and its 95% confidence interval) is based on the assumed risk in the comparison group and the <b>relative effect</b> of the intervention (and its 95% CI).</p> <p>CCT: computerised cognitive training; CI: confidence interval; MD: mean difference; SMD: standardised mean difference</p>	
<p>GRADE Working Group grades of evidence.</p> <p><b>High quality:</b> further research is very unlikely to change our confidence in the estimate of effect.</p> <p><b>Moderate quality:</b> further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p><b>Low quality:</b> further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</p> <p><b>Very low quality:</b> we are very uncertain about the estimate.</p>	

<sup>a</sup>The direction of the difference in effect was standardised so that lower values favour CCT and higher values favour control.

<sup>b</sup>Downgraded two levels for imprecision (confidence interval included effects that are not clinically relevant) and risk of bias.

<sup>c</sup>Downgraded three levels for imprecision (confidence interval included effects that are not clinically relevant), inconsistency (high heterogeneity), and risk of bias.

## DISCUSSION

### Summary of main results

#### Computerised cognitive training (CCT) compared to active control interventions at end of trial

All evidence addressing this comparison was of very low quality; therefore, we are not able to determine whether CCT has an effect on global cognitive function or on episodic memory, speed of processing, executive function, or working memory.

#### Computerised cognitive training (CCT) compared to inactive control at end of trial

We found low-quality evidence suggesting that when compared with an inactive control, CCT may slightly improve episodic memory and may have little or no effect on executive function, working memory, or verbal fluency. The quality of the evidence on speed of processing was very low, so we were unable to draw any conclusions about an effect of CCT on this outcome.

#### Overall completeness and applicability of evidence

Lack of long-term follow-up in the included studies does not allow examination of the effects of CCT on maintenance of cognitive function over time, as there has been insufficient time for age-related cognitive decline to occur.

We did not identify any trial that examined the outcomes quality of life, psychological well-being, daily functioning, or adverse events. These are all important outcomes for clinical decision-making and for potential consumers.

As we excluded a large number of studies from this review because the intervention was provided for less than 12 weeks ( $n = 132$ ; 42%), the extent to which trials of shorter duration may maintain or benefit cognitive function remains unanswered by this review. Furthermore, the results of this review cannot necessarily be generalised to shorter training regimens. For example, a review of computerised training in cognitively healthy elderly included 12 studies, nine of which provided training interventions of less than 12 weeks' duration, and found that five short training programmes resulted in cognitive improvement across several cognitive domains (Shao 2015).

#### Quality of the evidence

We identified several limitations in the included studies, and we rated none as having low risk of bias. We considered only two studies to have low risk of selection bias (Lampit 2014; Peretz 2011), and we considered none to have low risk of performance bias. We

judged that risk for, respectively, detection bias, attrition bias, and reporting bias was low in four studies (Desjardins-Crépeau 2016; Klusmann 2010; Lampit 2014; Legault 2011; Peretz 2011), three studies (Lampit 2014; Legault 2011; Shatil 2013), and six studies (Desjardins-Crépeau 2016; Klusmann 2010; Leung 2015; Peretz 2011; Shatil 2013; van der Reijndel 2014).

Overall, the quality of evidence was very low or low according to GRADE criteria, so we have low to very low confidence in the summary estimates of effects reported here. Identified issues with quality were due to imprecision, inconsistency between trials - which was highly considerable for most outcomes - and risk of bias. Higher-quality evidence is required if we are to draw conclusions with greater certainty.

#### Potential biases in the review process

We used an exhaustive search strategy covering multiple data sources, considering full reports, abstracts, and other report types described in any language. We deem it unlikely that we missed relevant trials. We searched for unpublished and ongoing data, but we identified published data only. We did not detect publication bias, but this does not mean that we can rule out publication bias. We could not formally assess it in funnel plot evaluations because of the small number of studies identified.

We applied sound methods to complete our review. Use of at least two independent review authors minimised bias at the review level and avoided transcription errors during data extraction. We followed Cochrane guidance and used a component approach to assess the methodological rigour of trials while applying GRADE to assess the quality of the overall body of evidence. We nevertheless are aware of some important limitations in this review. We had to choose a method to deal with the use of multiple instruments to measure a specific cognitive (sub)-domain within and across trials. We opted for use of a hierarchy that informed us which outcome data we should extract, so that for each cognitive outcome, data from a single validated instrument per trial contributed to analyses. The hierarchy of these outcomes can be consulted in the protocol of our review. As instruments differed across trials, we chose to use the standardised mean difference to combine outcome data across trials. An alternative strategy could have been to consider a single preferred instrument for each cognitive domain, using the mean difference to combine outcome data across trials. We preferred to use a hierarchy, so that we could include a larger number of trials. The disadvantage of our approach is that interpretation of effect size (standardised mean difference (SMD)) is less intuitive than results reported on a natural scale. As there is little consensus on the threshold for minimally clinically important differences, we refrained from translating estimates on the SMD back to the natural scale of, for example, the Mini Mental State Examination (MMSE). We may have introduced between-trial heterogeneity by combining SMDs derived from multiple instruments, but the small number of trials identified did not allow us to assess such

impact. As we had no access to individual participant data, we chose not to combine results on multiple instruments within a trial before combining results across trials, as this would put the summary estimates at high risk of ecological fallacy.

## Agreements and disagreements with other studies or reviews

Results from other meta-analyses and individual clinical trials are highly variable. The results from this review are similarly mixed and suggest small significant gains in information processing and possibly episodic memory, but no gains in terms of other cognitive outcomes. Other recent meta-analyses of computerised cognitive programmes with no minimum training duration showed improvement in executive function, global composite scores, memory, and processing speed compared to controls and in non-cognitive outcomes including emotional well-being and everyday functioning (e.g. [Gates 2011a](#); [Gordon 2013](#); [Kelly 2014a](#); [Kueider 2012](#); [Lampit 2014](#); [Rebok 2014](#); [Shao 2015](#)).

However, overall evidence from these trials in cognitively healthy adults is mixed, and opposing professional views regarding the evidence base have been published ([Lampit 2015](#); [Ratner 2015](#)). We identified a rather large number of reviews relative to the limited number of well-designed clinical trials. Additionally, diversity of interventions involving dose, duration, and intensity of cognitive training, along with methodological constraints such as lack of randomisation, small samples, and lack of blinding, may account for the disparate results ([Gates 2010](#); [Kueider 2012](#); [Mowszowski 2010](#); [Papp 2009](#); [Shao 2015](#); [Steiner 2010](#)).

## AUTHORS' CONCLUSIONS

### Implications for practice

At the current time, there is a lack of high-quality evidence to show that computerised cognitive function (CCT) for 12 or more weeks improves cognition in healthy older adults. Despite our intention to examine generalisation of effects to objective measures of everyday functioning, we are able to comment only on transfer of training effects to cognitive outcomes.

Clinicians and consumers may find the field confusing with contradictory messages about research evidence and divisive debates in the research community (e.g. [Lampit 2015](#); [Ratner 2015](#)). Fear of developing dementia is a significant health concern of older adults, and there is increasing demand for interventions to address age-related and non-pathological cognitive decline. This goes along with the development and commercialisation of brain training products targeting older consumers. Although we conclude in this review that we are uncertain whether CCT has any effect on cognitive functioning, five of the eight included studies lasted

just three months, and it remains possible that longer-term studies could show benefit for maintaining cognitive function. The potential for training to help maintain older adults' abilities in the future largely remains untested, although it is hypothesised that those who participate in training are less likely to show decline over the longer term than those who receive no training.

### Implications for research

Studies of CCT in cognitively healthy adults could be improved by careful consideration given to study design, including choice and measurement of outcomes and time points of follow-up. Selection of outcomes ought to address the principal objective of CCT - not only that training benefits the specific skills trained but also that those benefits *transfer* to improvement or maintenance of function on non-trained cognitive tasks, and *generalise* to non-cognitive domains such as daily functioning ([Kelly 2014a](#)), although the topic of transfer is debated ([Zelinski 2009](#)). In this review, we found that measures of functional performance that may indicate generalisation were absent from the identified studies. Inclusion of outcomes that could demonstrate effects on quality of life, psychiatric symptoms, mood, and daily functioning should be encouraged in future studies.

To accurately measure change in cognitive function, and to identify transfer and generalisation, selected outcomes should be sensitive to subtle and possibly non-linear changes, should have high reliability, should have alternate forms or be psychometrically robust for repeated use, and should have low risk of floor and ceiling effects. This is particularly relevant for cognitively healthy adults, in whom ceiling effects may dominate (i.e. how do you improve on normal?). We advocate for establishment of an international multi-disciplinary panel to develop a standardised core outcome set for cognitive assessments in older individuals with and without cognitive decline, to improve outcome reporting and facilitate evidence synthesis. Ideally, studies should measure change immediately after an intervention ends and then should monitor function over time. Future research studies should move towards investigating different types of training exercises, differential effects of training on separate cognitive domains, and the impact of variability in the frequency, intensity, and duration of interventions. Furthermore, it would be helpful to assess effectiveness of training in realistic situations, including participants with health risk factors, comorbidities, and barriers to participation. Inactive controls are suitable for research examining possible neuroplastic mechanisms and brain reserve, and for inclusion in simple efficacy studies, and the clinical effectiveness and comparative studies described above will require an active control arm.

We found no evidence of an effect on global cognitive function when CCT was compared to active control interventions. Global cognition measured on screening tests may fail to capture changes in general intellectual functions and will be insensitive to changes in specific cognitive domains.

Finally, absent from most clinical trials of CCT is longitudinal measurement. Although no improvement in global cognition was evident at end of trial, the possibility of maintained function over time remains unknown because of lack of follow-up. Neuroplastic changes, alterations to brain reserve, and generalisation to daily functions will naturally require a longer time course. For example, the ACTIVE trial clearly demonstrates that beneficial changes in IADL, driving, and mental health occur over several years (Zelinski 2009).

Improved reporting of study methods should be a priority because of the high proportion of unclear risks of bias, which could be improved through simple steps, such as adherence to CONSORT, improved data management to reduce the quantity of incomplete data, and development of methods to facilitate blinding of participants and personnel. Blinding of participants is especially important given the commercialisation of CCT, advertisements, and widespread community exposure, and an active control may partially address this potential bias.

Computerised cognition training has the potential to be introduced as a preventive intervention both to reduce cognitive decline and to improve cognitive function for adults in late life. At this stage, there remains a paucity of methodologically meaningful research in this group of individuals.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

#### Desjardins-Crépeau 2016

Methods	<ul style="list-style-type: none"> <li>• <b>Design:</b> 2 × 2 factorial RCT design</li> <li>• <b>Recruitment period:</b> not reported</li> <li>• <b>No. of centres involved:</b> not reported</li> <li>• <b>Unit of randomisation:</b> individuals</li> <li>• <b>No. randomised:</b> 136 participants</li> <li>• <b>Number of arms considered in this review:</b> 4</li> <li>• <b>Maximum trial duration:</b> 12 weeks.</li> <li>• <b>Funding by non-profit organisation:</b> this study was supported by a Canadian Institutes of Health Research (CIHR) grant (#187596). One study author was supported by a doctoral fellowship from the CIHR, and the other study author was supported by the Canada Research Chair Programme</li> <li>• <b>Funding by commercial organisation:</b> none reported</li> <li>• <b>Publication status:</b> full-text report</li> </ul>
Participants	<ul style="list-style-type: none"> <li>• <b>Patient flow:</b> 136 participants were randomised, 91 completed the programme, and 76 were considered in the report. Each of 38 participants had aerobic and resistance (AR) and stretching and toning (ST) exercises. Of these, 22 in AR and 20 in ST received the computerised stimulation (experimental group), and 16 in AR and 18 in ST received computer lessons (control group), respectively</li> <li>• <b>Number of females:</b> arm with AR: 13 of 22 (59%) in experimental group, 8 of 16 (50%) in control group; arm with ST: 17 of 20 (85%) in experimental group, 15 of 18 (83%) in control group</li> <li>• <b>Average age (SD):</b> arm with AR: 72.7 (7.4) years in experimental group, 70.9 (7.4) years in control group; arm with ST: 73.2 (6.3) years in experimental group, 72.5 (7.0) years in control group</li> <li>• <b>Average (SD) education:</b> arm with AR: 14.4 (2.8) years in experimental group, 15.9 (2.1) years in control group; arm with ST: 14.1 (4.3) years in experimental group, 14.1 (3.8) years in control group</li> <li>• <b>Baseline cognitive function:</b> MMSE in arm with AR: 28.8 (1.3) in experimental group, 28.8 (1.0) in control group; MMSE in arm with ST: 29.4 (0.7) in experimental group, 28.5 (1.4) in control group</li> <li>• <b>Selection criteria on cognition:</b> community-dwelling participants were recruited from public advertisements (years and newspapers) and from the research centre's participant pool. A telephone-based screening interview was used to assess the eligibility of each candidate. Exclusion criteria were as follows: history of neurological disease or major surgery in the year preceding the study, auditory or visual impairments that were not corrected, smoking, severe mobility limitations, any other contraindication to perform physical activity, currently engaged in any type of structured physical activity, high score on geriatric depression scale, &lt; 60 years old</li> <li>• <b>Ethnicity:</b> not reported</li> <li>• <b>APOE:</b> number of participants positive for APOE not reported</li> </ul>

Interventions	<p><b>Type of experimental intervention:</b> computerised cognitive training group; treatment duration 12 weeks; intervention provided in small group format under supervision of a neuropsychologist student</p> <ul style="list-style-type: none"> <li>• <b>Details of experimental intervention:</b> each weekly session of dual task (DT) training took place in a room with 10 computer stations and was supervised by a student in neuropsychology. Participants were trained on a computerised visual DT analog. The task consisted of 2 visual discrimination tasks performed separately and concurrently. The first task was a number discrimination task (3, 5, and 8), and the second was a shape discrimination task (circle, square, and diamond). Participants had to respond to the number or shape presented on the screen with a key press on the appropriate button identified on the keyboard. The DT consisted of 4 different blocks, each containing different types of trials</li> <li>• <b>Type of concomitant treatment provided:</b> arm with AR: included two 60-minute sessions/week for 12 weeks of physical exercise of cardiorespiratory fitness and lower body muscle strength; arm with ST included two 60-minute sessions/week for 12 weeks of series of exercises aimed at improving flexibility and general motor skills without a specific focus on increasing cardiorespiratory capacity or strength</li> <li>• <b>Session duration:</b> 60 minutes in the experimental group</li> <li>• <b>Number of treatment sessions:</b> 12 in the experimental group</li> <li>• <b>Treatment frequency:</b> 1 session per week</li> <li>• <b>Maximum treatment duration in weeks:</b> 12 in the experimental group</li> </ul> <p><b>Type of control intervention:</b> inactive; treatment duration of 12 weeks; intervention provided in group format, under supervision</p> <ul style="list-style-type: none"> <li>• <b>Details of control intervention:</b> computer lessons (control) condition consisted of introductory exercises to computers and diverse software (e.g. Word, Excel), as well as an introduction to the Internet (search engines, websites, online games, etc.). These sessions took place in the same computer room as the DT training programme and were taught by a student in neuropsychology</li> <li>• <b>Type of concomitant treatment provided:</b> arm with AR: included two 60-minute sessions/week for 12 weeks of physical exercise of cardiorespiratory fitness and lower body muscle strength; arm with ST included two 60-minute sessions/week for 12 weeks of series of exercises aimed at improving flexibility and general motor skills without a specific focus on increasing cardiorespiratory capacity or strength</li> <li>• <b>Session duration:</b> 60 minutes in the control group</li> <li>• <b>Number of treatment sessions:</b> 12 in the control group</li> <li>• <b>Treatment frequency:</b> 1 session per week</li> <li>• <b>Maximum treatment duration in weeks:</b> 12 in the control group</li> </ul>
Outcomes	<ul style="list-style-type: none"> <li>• <b>Cognitive functioning outcomes considered</b> <ul style="list-style-type: none"> <li>◦ Episodic memory measured with Rey Auditory Verbal Learning Test, delayed at 12 weeks, on a scale from 0 to 15, with higher values indicating benefit</li> <li>◦ Executive function measured in seconds with the Color-Word Interference Test (CWIT-switching) of the Delis-Kaplan Executive Functions System is based on the Stroop procedure at 12 weeks on a scale from not reported to not reported with lower values indicating benefit</li> <li>◦ Speed of processing measured with TMT-A at 12 weeks on a scale from not reported to not reported with lower values indicating benefit</li> </ul> </li> <li>• <b>Physical functioning outcome considered:</b> none reported</li> <li>• <b>Quality of life outcome considered:</b> none reported</li> </ul>

	<ul style="list-style-type: none"><li>• <b>Safety outcome considered:</b> none reported</li><li>• <b>Depression outcome considered:</b> none reported</li><li>• <b>Other outcome data on cognitive functioning, not considered in our meta-analyses</b><ul style="list-style-type: none"><li>◦ Episodic memory measured with Rey Auditory Verbal Learning Test, total 5 trials and immediate recall at 12 weeks, on a scale from not reported to not reported with higher values indicating benefit</li><li>◦ Executive function measured in seconds with the Color-Word Interference Test (CWIT-inhibition) of the Delis-Kaplan Executive Functions System is based on the Stroop procedure, TMT part B at 12 weeks on a scale from not reported to not reported with lower values indicating benefit</li><li>◦ Executive function measured in seconds with BDT-DT index at 12 weeks on a scale from not reported to not reported with higher values indicating benefit</li><li>◦ Speed of processing measured in seconds with the Color-Word Interference Test (CWIT-color naming and seconds) of the Delis-Kaplan Executive Functions System is based on the Stroop procedure and BDT-simple tasks at 12 weeks in seconds, with lower values indicating benefit</li></ul></li></ul>	
Notes	<p>This study was supported by a Canadian Institutes of Health Research (CIHR) grant (#187596). One study author was supported by a doctoral fellowship from the CIHR, and another study author was supported by the Canada Research Chair Program. Study authors report no conflict of interest in the study</p> <p>We combined data from ST and AR arms</p>	
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	<b>Judgement:</b> adequate random sequence generation <b>Quote(s):</b> “the study was carried on in waves of 16-32 participants randomly assigned to one of the four training combinations using the website randomization.com”
Allocation concealment (selection bias)	Unclear risk	<b>Judgement:</b> method of allocation concealment not reported <b>Quote(s):</b> “the study was carried on in waves of 16-32 participants randomly assigned to one of the four training combinations using the website randomization.com”
Blinding of participants (performance bias)	High risk	<b>Judgement:</b> blinding not feasible
Blinding of personnel (performance bias)	High risk	<b>Judgement:</b> blinding not feasible

Blinding of outcome assessment (detection bias) All outcomes	Low risk	<b>Judgement:</b> explicit reporting of blinded outcome assessment <b>Quote(s):</b> “the evaluators at both pretest and posttest were blind to the group membership of participants”
Incomplete outcome data (attrition bias) All outcomes	High risk	<b>Judgement:</b> we judged high risk of bias, as on average less than 90% of randomised participants were analysed <b>Quote(s):</b> “among the 125 participants who were enrolled in the study, 91 participants completed the program. Among those, three participants failed to participate in the posttest evaluations and two participants had invalid data due to illness at posttest examinations and were thus excluded from analyses”
Selective reporting (reporting bias)	Low risk	<b>Judgement:</b> all outcomes described in the methods section are adequately addressed in the results section
Other bias	Low risk	<b>Judgement:</b> no other sources of bias detected

## Klusmann 2010

Methods	<ul style="list-style-type: none"> <li>• <b>Design:</b> 3-arm RCT with parallel-group design</li> <li>• <b>Recruitment period:</b> 2006 to 2008</li> <li>• <b>No. of centres involved:</b> not reported</li> <li>• <b>Unit of randomisation:</b> individuals</li> <li>• <b>No. randomised:</b> 259</li> <li>• <b>Number of arms considered in this review:</b> 2</li> <li>• <b>Maximum trial duration:</b> 7 months</li> <li>• <b>Funding by non-profit organisation:</b> German Research Foundation (grant number 429) Doctoral Programme “Neuropsychiatry and Neuropsychology of Aging” (years covered: 2006 to 2008) to I.H. and the Gertrud and Hugo Adler Foundation (years covered: 2006 to 2008)</li> <li>• <b>Funding by commercial organisation:</b> none reported</li> <li>• <b>Publication status:</b> full-text report</li> </ul>
Participants	<ul style="list-style-type: none"> <li>• <b>Patient flow:</b> 92 randomised, 92 described at baseline in experimental group; 76 randomised, 76 described at baseline in control group</li> <li>• <b>Number of females:</b> 92 of 92 (100%) in experimental group 1; 76 of 76 (100%) in control group</li> <li>• <b>Average age (SD):</b> 74 (4.4) years in experimental group 1; 74 (4.3) years in control group</li> <li>• <b>Average (SD) education:</b> 12 (2.6) years in experimental group; 12 (2.8) years in control group</li> </ul>

	<p>control group</p> <ul style="list-style-type: none"> <li>● <b>Baseline cognitive function:</b> baseline cognitive function measured with: selection criteria on cognition overall: participants were screened to rule out the presence of cognitive impairment or depression and were included if they made no more than 4 errors on the Mini Mental State Examination (MMSE; 20) and scored less than 6 points on the 15-item short-form Geriatric Depression Scale (GDS-Sf; 21). Baseline mean MMSE (SD) was 28.76 (0.97)</li> <li>● Selection criteria on cognition in experimental group: participants were screened to rule out the presence of cognitive impairment or depression and were included if they made no more than 4 errors on the Mini Mental State Examination (MMSE; 20) and scored less than 6 points on the 15-item short-form Geriatric Depression Scale (GDS-Sf; 21). Baseline mean MMSE (SD): 28.84 (0.94)</li> <li>● <b>Selection criteria on cognition in control group:</b> participants were screened to rule out the presence of cognitive impairment or depression and were included if they made no more than 4 errors on the Mini Mental State Examination (MMSE; 20) and scored less than 6 points on the 15-item short-form Geriatric Depression Scale (GDS-Sf; 21). Mean baseline MMSE (SD): 28.62 (1.08)</li> <li>● <b>Ethnicity:</b> not reported</li> <li>● <b>APOE:</b> number of participants positive for APOE not reported</li> </ul>
Interventions	<p><b>Type of experimental intervention:</b> computerised CT individualised; treatment duration of 26 weeks; intervention provided as individual training, under supervision</p> <ul style="list-style-type: none"> <li>● <b>Details of experimental intervention:</b> the computer course covered heterogeneous and multi-faceted tasks such as learning how to operate with common software and hardware, writing, playing, calculating, surfing on the Internet, emailing, drawing, image editing, and videotaping</li> <li>● <b>Session duration:</b> 90 minutes in experimental group</li> <li>● <b>Number of treatment sessions:</b> 75 in experimental group</li> <li>● <b>Treatment frequency:</b> not reported in experimental group</li> <li>● <b>Maximum treatment duration in weeks:</b> 26 in experimental group</li> </ul> <p><b>Type of control intervention:</b> inactive; duration of 26 weeks; without supervision</p> <ul style="list-style-type: none"> <li>● <b>Details of control intervention:</b> usual daily life/care</li> <li>● <b>Type of concomitant treatment provided:</b> none reported</li> <li>● <b>Session duration:</b> not reported in control group</li> <li>● <b>Number of treatment sessions:</b> not reported in control group</li> <li>● <b>Maximum treatment duration in weeks:</b> 26 in control group</li> </ul>
Outcomes	<ul style="list-style-type: none"> <li>● <b>Cognitive functioning outcomes considered</b> <ul style="list-style-type: none"> <li>○ Episodic memory measured with Rivermead Behavioural Memory Test (RBMT), delayed story recall at 6.5 months, on a scale from 0 to not reported with higher values indicating benefit*</li> <li>○ Executive functioning measured with Stroop test at 6.5 months, on a scale from not reported to not reported with higher values indicating benefit</li> <li>○ Verbal fluency measured with semantic verbal fluency at 6.5 months, on a scale from 0 to not reported with higher values indicating benefit</li> </ul> </li> <li>● <b>Physical functioning outcome considered:</b> none reported</li> <li>● <b>Quality of life outcome considered:</b> none reported</li> <li>● <b>Safety outcome considered:</b> none reported</li> <li>● <b>Depression outcome considered:</b> none reported</li> </ul>

	<ul style="list-style-type: none"><li>● <b>Other outcome data on cognitive functioning, not considered in our meta-analyses</b><ul style="list-style-type: none"><li>○ Episodic memory measured with Rivermead Behavioural Memory Test (RBMT), immediate story recall at 6.5 months, on a scale from 0 to not reported with higher values indicating benefit*</li><li>○ Episodic memory measured with Free and Cued Selective Reminding Test (FCSRT), short delay at 6.5 months, on a scale from 0 to 48 with higher values indicating benefit</li><li>○ Episodic memory measured with Free and Cued Selective Reminding Test (FCSRT), long delay at 6.5 months, on a scale from 0 to 16 with higher values indicating benefit</li><li>○ Executive function measured with Trail Making Test (TMT)-B/A at 6.5 months, on a scale from not reported to not reported with lower values indicating benefit</li></ul></li></ul> <p>*Our hierarchy did not indicate a preference for the delayed subscale over the immediate subscale. Whenever both immediate and delayed subscales were available, the delayed subscale was included in the meta-analyses</p>	
Notes	Baseline characteristics were reported for the randomised population, whereas outcome data are presented only for those with pretest and post-test evaluations	
<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	<b>Judgement:</b> adequate random sequence generation <b>Quote(s):</b> “the randomization sequence for each of the seven study cohorts was generated using Research Randomizer (www.randomizer.org) by VK”
Allocation concealment (selection bias)	Unclear risk	<b>Judgement:</b> envelopes were not reported to be opaque. Although preparation of envelopes was done centrally by an independent research assistant, we are unsure if the nurse who was in charge of handing over the envelopes could foresee the codes kept in the envelopes <b>Quote(s):</b> “a study assistant prepared seven sets of 34 numbered envelopes containing the accordant randomization results (12 for the intervention groups each and 10 for the control group)”; “the sealed envelopes, all prepared before starting the examination of the first cohort and kept locked in a safe deposit box, were given on a daily basis to the study nurse in consecutive order. En-



		velopes were opened after the main part of the clinical baseline evaluation to have the participants of the exercise group undergo the additional stress ECG. If study candidates withdrew from the study or were excluded because of lacking eligibility criteria at a later point in time, the study assistant prepared additional envelopes containing the corresponding assignments of those who dropped out in the sequence of deposit”
Blinding of participants (performance bias)	High risk	<b>Judgement:</b> patients were not blinded to the treatment assigned <b>Quote(s):</b> “before participants were informed about their group assignment, at a second 2.5-hour appointment”; “finally, we used a single-, not a double-, blind design. However, to design a “placebo” control group would be methodologically challenging and, furthermore, to keep participants fully blinded would raise ethical questions”
Blinding of personnel (performance bias)	High risk	<b>Judgement:</b> blinding not feasible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<b>Judgement:</b> explicit reporting of blinded outcome assessment. Therapists were also outcome assessors <b>Quote(s):</b> “participants and neuropsychological assessors were blinded to group allocation up to the completed baseline examination of the whole cohort (double blind) ; participants were then informed by mail. Assessors were kept blind at post-test by explicitly instructing the participants not to discuss any of the information regarding randomization and intervention with the research staff conducting the testing”
Incomplete outcome data (attrition bias) All outcomes	High risk	<b>Judgement:</b> we judged high risk of bias, as on average less than 90% of randomised participants were analysed <b>Quote(s):</b> “259 participants to be randomized (91 for the exercise, 92 for the computer, and 76 for the control condition), of whom 12 participants (5 of the exercise and 7 of the computer condition) refused to participate after being informed about

		their group assignment and withdrew consent before treatment started. Thus, 247 (95.4% of randomized participants; ie, 86 for the exercise, 85 for the computer, and 76 for the control condition) women were allocated to the corresponding groups, of whom 230 (93.1% of baseline, 88.8% of randomized) returned for follow-up"; "three women of the computer group were excluded from analyses of pre-post change in one cognitive test each, due to incorrect test data assessment"
Selective reporting (reporting bias)	Low risk	<b>Judgement:</b> all outcomes described in the methods section are adequately addressed in the results section
Other bias	Low risk	<b>Judgement:</b> no other sources of bias were detected

# Lampit 2014

Methods	<ul style="list-style-type: none"> <li>• <b>Design:</b> 2-arm RCT with parallel-group design</li> <li>• <b>Recruitment period:</b> 2011 to 2012</li> <li>• <b>No. of centres involved:</b> 1</li> <li>• <b>Unit of randomisation:</b> individuals</li> <li>• <b>No. randomised:</b> 80</li> <li>• <b>Number of arms considered in this review:</b> 2</li> <li>• <b>Maximum trial duration:</b> 15 months</li> <li>• <b>Funding by non-profit organisation:</b> this study was funded by the Dementia Collaborative Research Centres (DCRC) - Assessment and Better Care (ID PDCRC-CB50), in which HB is the director, as well as the Dreikurs Bequest. MV is a National Health and Medical Research Council of Australia Career Development Fellow (ID 1004156)</li> <li>• <b>Funding by commercial organisation:</b> none reported</li> <li>• <b>Publication status:</b> full-text report</li> </ul>
Participants	<ul style="list-style-type: none"> <li>• <b>Patient flow:</b> 41 randomised, 39 described at baseline in experimental group; 39 randomised, 38 described at baseline in control group</li> <li>• <b>Number of females:</b> 29 of 39 (74%) in experimental group 1; 24 of 38 (63%) in control group</li> <li>• <b>Average age (SD):</b> 72 (7.1) years in experimental group 1; 72 (5.3) years in control group</li> <li>• <b>Education:</b> experimental group 1: low education (<math>\leq 10</math> years), 11/39 (28.2); control: low education (<math>\leq 10</math> years), 11/38 (29%)</li> <li>• <b>Baseline cognitive function:</b> MMSE scores ranged from 24 to 30 (mean MMSE 28, SD 1.6). All participants had at least 1 established dementia risk factor, the most prevalent being subjective memory complaints (68.9% in women; 70.1% in men)</li> <li>• <b>Selection criteria on cognition:</b> intervention group: MMSE (SD): 28.2 (1.4).</li> </ul>

	<p>All participants had at least 1 established dementia risk factor, the most prevalent being subjective memory complaints (69%), hypertension (31%), hypercholesterolaemia (36%). Control group: MMSE (SD): 27.8 (1.8). All participants had at least 1 established dementia risk factor, the most prevalent being subjective memory complaints (71%), hypertension (53%), hypercholesterolaemia (37%)</p> <ul style="list-style-type: none"> <li>• <b>Ethnicity:</b> not reported.</li> <li>• <b>APOE:</b> number of participants positive for APOE not reported</li> </ul>
Interventions	<p><b>Type of experimental intervention:</b> computerised CT group; treatment duration of 12 weeks; intervention provided in group format, under supervision</p> <ul style="list-style-type: none"> <li>• <b>Details of experimental intervention:</b> 24 exercises from the COGPACK package, version 8.1 (Marker Software), to cover the 5 cognitive domains: memory, attention, response speed, executive functions, and language</li> <li>• <b>Type of concomitant treatment provided:</b> none reported</li> <li>• <b>Session duration:</b> 30 to 45 minutes in experimental group</li> <li>• <b>Number of treatment sessions:</b> 36 in experimental group</li> <li>• <b>Treatment frequency:</b> 3/week in experimental group</li> <li>• <b>Maximum treatment duration in weeks:</b> 12 in experimental group</li> </ul> <p><b>Type of control intervention:</b> other; treatment duration of 12 weeks; intervention provided in group format, under supervision</p> <ul style="list-style-type: none"> <li>• <b>Details of control intervention:</b> this control intervention was developed for general sensorimotor stimulation, computer use, socialisation, motivation, simple learning and memory demands, and other non-specific effects inherent to supervised CCI, and was used in a previous trial conducted by this group. Participants viewed 7 <i>National Geographic</i> videos per session on computer and answered multiple choice questions immediately after each presentation</li> <li>• <b>Type of concomitant treatment provided:</b> none reported</li> <li>• <b>Session duration:</b> 30 to 45 minutes in control group</li> <li>• <b>Number of treatment sessions:</b> 36 in control group</li> <li>• <b>Treatment frequency:</b> 3/week in control group</li> <li>• <b>Maximum treatment duration in weeks:</b> 12 in control group</li> </ul>
Outcomes	<ul style="list-style-type: none"> <li>• <b>Cognitive functioning outcomes considered</b> <ul style="list-style-type: none"> <li>◦ Global cognitive functioning measured with composite score of memory, speed, and executive function at 3 and 15 months, on a scale from not reported to not reported with higher values indicating benefit</li> </ul> </li> <li>• <b>Physical functioning outcome considered:</b> none reported</li> <li>• <b>Quality of life outcome considered:</b> none reported</li> <li>• <b>Safety outcome considered:</b> none reported*</li> <li>• <b>Depression outcome considered:</b> none reported</li> <li>• <b>Other outcome data on cognitive functioning, not considered in our meta-analyses:</b> none reported</li> </ul> <p>*Study authors reported: "no adverse effects related to the intervention were recorded throughout the study period". As this is about attributed AEs only, we did not consider the data</p>
Notes	<p>Timecourse Trial. ACTRN12611000702910. The funding panel had no role in study design, data collection, data analysis, interpretation of data, writing of the report, or the decision to submit the paper for publication. There were also no systematic differences</p>

	in protocol adherence in the CCI group (35.1 sessions, 97.5%) compared to the AC training group (34.7 sessions, 96.4%; P = 0.581)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<b>Judgement:</b> adequate random sequence generation <b>Quote(s):</b> “participants were randomised using a simple computer-generated randomisation sequence in a 1:1 ratio to either CCI or active control (AC) group”; from trial registration: “simple randomisation table created by a computer software”
Allocation concealment (selection bias)	Low risk	<b>Judgement:</b> allocation was done by the principal investigator, who does not seem to be involved with training or outcome assessment, and seems to be independent. Randomisation was organised centrally, and for this reason, we judged central randomisation <b>Quote(s):</b> “randomisation was conducted by the principal investigator (MV) and was concealed from the rest of the research team until the first day of training”; from trial registration: “allocation involved contacting the holder of the allocation schedule who was ”off-site“ or at central administration site”
Blinding of participants (performance bias)	Low risk	<b>Judgement:</b> an attempt was made to blind participants, as the 2 types of interventions were distinguishable, but as participants were blinded to the study hypothesis, we deem it likely that blinding was successful <b>Quote(s):</b> “participants were blinded to the study hypotheses. On-going participant blinding achieved by describing CCI as a ”diversified set of cognitive exercises“, and AC as comprehension and memory exercises”
Blinding of personnel (performance bias)	High risk	<b>Judgement:</b> blinding of therapists not feasible

Blinding of outcome assessment (detection bias) All outcomes	Low risk	<b>Judgement:</b> outcome assessors explicitly reported to be blinded <b>Quote(s):</b> “assessors were blinded to group allocation”
Incomplete outcome data (attrition bias) All outcomes	Low risk	<b>Judgement:</b> for the outcome global cognitive functioning: 39 out of 41 (95%) randomised were analysed in experimental group, and 38 out of 39 (97%) randomised were analysed in control group. Statistical analyses were reported to be done according to the intent-to-treat principle. In the experimental group, 15/41 participants were not evaluated 12 months post training. In the control group, 10/39 patients were not evaluated 12 months post training. Although study authors reported that this was an intention-to-treat (ITT) analysis, they deemed the fraction of missing data was too large. MMRM incorporates a model for missing data values and so avoids discrete imputation or omission of cases. All analyses are therefore ITT. Twelve participants withdrew during the intervention period (8 in the CCI group, 4 in the AC group; 2-sided $\chi^2$ $P = 0.347$ ), and 10 additional participants (5 in each group) were lost to longitudinal follow-up (see Figure 1). No baseline sociodemographic or clinical differences were noted between dropouts and those who completed the intervention
Selective reporting (reporting bias)	High risk	<b>Judgement:</b> all outcomes described in the methods section are adequately addressed in the results section, but on the trial registration site, an additional primary outcome is listed that is described as post-hoc testing in the full publication. In addition, 2 instruments were dropped due to lack of feasibility <b>Quote(s):</b> “trial registration: first primary outcome (out of 2) - scores in (1) a computer-based adaptation of WAIS 4 Matrix Reasoning test; (2) Controlled Oral Word Association Test (COWAT); (3) Boston Naming Test (short versions); and (4) a computerised adaptation of the Recognition Memory Test and full text: These 4

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		tests were included in the more expansive post hoc Global Cognitive Score and full text: one test was initially planned but not implemented because of poor usability with our participants (Mindstreams Visual-Spatial Orientation test), and another test (Cogscreen) could not be implemented because of technical issues. These changes were documented in the trial registry”
Other bias	Low risk	<b>Judgement:</b> no other sources of bias were detected

**Legault 2011**

Methods	<ul style="list-style-type: none"> <li>● <b>Design:</b> 4-arm randomised single-blinded controlled trial with 2 × 2 factorial design</li> <li>● <b>Recruitment period:</b> 2008 to 2009</li> <li>● <b>No. of centres involved:</b> 1</li> <li>● <b>Unit of randomisation:</b> individuals</li> <li>● <b>No. randomised:</b> 73</li> <li>● <b>Number of arms considered in this review:</b> 4</li> <li>● <b>Maximum trial duration:</b> 4 months</li> <li>● <b>Funding by non-profit organisation:</b> Department of Health and Human Services, National Institutes of Health (1R01AG029285 - 01A1), and the General Clinical Research Center of Wake Forest University Baptist Medical Center (M01-RR07122)</li> <li>● <b>Funding by commercial organisation:</b> none reported</li> <li>● <b>Publication status:</b> full-text report</li> </ul>
Participants	<ul style="list-style-type: none"> <li>● <b>Patient flow:</b> 18 randomised, 18 described at baseline in experimental group; 18 randomised, 18 described at baseline in control group</li> <li>● <b>Number of females:</b> 8 of 18 (44%) in experimental group 1; 7 of 18 (38%) in control group 1</li> <li>● <b>Average age (SD):</b> 76 (5.2) years in experimental group 1; 75 (4.8) years in control group 1</li> <li>● <b>Education:</b> experimental group 1: high school or less: 4 (22%), more than high school: 14 (78%); control group 1: high school or less: 5 (28%), more than high school: 13 (72%)</li> <li>● <b>Baseline cognitive function:</b> experimental group 1: selection criteria on cognition overall: community-dwelling persons, aged 70 to 85 years, who were at risk for cognitive decline but who did not have mild cognitive impairment <ul style="list-style-type: none"> <li>● Selection criteria on cognition in experimental group: community-dwelling persons, aged 70 to 85 years, who were at risk for cognitive decline but who did not have mild cognitive impairment. Control group: community-dwelling persons, aged 70 to 85 years, who were at risk for cognitive decline but who did not have mild cognitive impairment</li> </ul> </li> <li>● <b>Ethnicity:</b> experimental group: 17 white, 0 Indian, 0 Asian, 1 black, 0 other, 0</li> </ul>

	<p>unclear; control group: 17 white, 0 Indian, 0 Asian, 1 black, 0 other, 0 unclear</p> <ul style="list-style-type: none"> <li>● <b>Genetic marker:</b> experimental group: present: 2 (17%), absent: 10 (83%); control group: present: 3 (25%), absent: 9 (75%)</li> </ul>
Interventions	<p><b>Type of experimental intervention:</b> computerised CT group; treatment duration of 17.2 weeks; intervention provided in small group format under supervision</p> <ul style="list-style-type: none"> <li>● <b>Details of experimental intervention:</b> sessions were centre-based, conducted via computer, carried out with small groups of no more than 6 individuals, and monitored by skilled trainers. For each session, participants studied a list of 30 words, followed by a recognition test consisting of 30 studied words and 30 new words with each new word repeated once, and were asked to respond “yes” to study words and “no” to new items both times they occurred</li> <li>● <b>Type of concomitant treatment provided:</b> none in comparison 1; physical activity in comparison 2</li> <li>● <b>Session duration:</b> 10 to 12 minutes in experimental group</li> <li>● <b>Number of treatment sessions:</b> 24 in experimental group</li> <li>● <b>Treatment frequency:</b> training consisted of 4 consecutive 10- to 12-minute sessions per day, administered 2 times per week for 2 months, which then tapered to 1 time per week for 2 additional months in experimental group</li> <li>● <b>Maximum treatment duration in weeks:</b> 17.2 in experimental group</li> </ul> <p><b>Type of control intervention:</b> inactive; treatment duration of 17.2 weeks; intervention provided in group format, under supervision</p> <ul style="list-style-type: none"> <li>● <b>Details of control intervention:</b> Healthy Aging Education control intervention consisted of weekly lectures based on health education and was based on a programme developed originally at Stanford and adapted for the Lifestyle interventions and Independence for Elders pilot trial. Topics such as medications, foot care, travelling, and nutrition were covered</li> <li>● <b>Type of concomitant treatment provided:</b> none in comparison 1; physical activity in comparison 2</li> <li>● <b>Session duration:</b> not reported in control group</li> <li>● <b>Number of treatment sessions:</b> not reported in control group</li> <li>● <b>Treatment frequency:</b> 1/week in control group</li> <li>● <b>Maximum treatment duration in weeks:</b> 17.2 in control group</li> </ul>
Outcomes	<ul style="list-style-type: none"> <li>● <b>Cognitive functioning outcomes considered for both comparisons</b> <ul style="list-style-type: none"> <li>○ Episodic memory measured with Logical Memory task from the Wechsler Memory Scale-III (LM2), Recall Total Score at 4 months, on a scale from 0 to not reported with higher values indicating benefit</li> <li>○ Executive functioning measured with Trails B Time-Trails A Time at 4 months, on a scale from 0 to not reported with lower values indicating benefit</li> </ul> </li> <li>● <b>Physical functioning outcome considered:</b> none reported</li> <li>● <b>Quality of life outcome considered:</b> none reported</li> <li>● <b>Safety outcome considered:</b> none reported</li> <li>● <b>Depression outcome considered:</b> none reported</li> <li>● <b>Other outcome data on cognitive functioning, not considered in our meta-analyses</b> <ul style="list-style-type: none"> <li>○ Episodic memory measured with Logical Memory task from the Wechsler Memory Scale-III (LM1) - Supplemental Score, 1st Recall at 4 months, on a scale from 0 to not reported with higher values indicating benefit</li> </ul> </li> </ul>

	<ul style="list-style-type: none"><li>○ Episodic memory measured with Hopkins Verbal Learning Test (HVLT), immediate recall at 4 months, on a scale from 0 to not reported with higher values indicating benefit</li><li>○ Episodic memory measured with Hopkins Verbal Learning Test (HVLT), delayed recall at 4 months, on a scale from 0 to not reported with higher values indicating benefit</li><li>○ Executive functioning measured with Flanker Task, Incongruent-Congruent RTs at 4 months, on a scale from 0 to not reported with higher values indicating benefit</li><li>○ Executive functioning measured with Task Switching, Switch-Non-switch RTs at 4 months, on a scale from 0 to not reported with higher values indicating benefit</li><li>○ Executive functioning measured with Self-Ordered Pointing Task, % correct at 4 months, on a scale from 0 to not reported with higher values indicating benefit</li><li>○ Executive functioning measured with 1-Back, % Hits-False Alarms at 4 months, on a scale from 0 to not reported with higher values indicating benefit</li><li>○ Executive functioning measured with 2-Back, % Hits-False Alarms at 4 months, on a scale from 0 to not reported with higher values indicating benefit</li></ul>	
Notes	As we pooled outcome data from the 2 comparisons within the trial, before pooling across trials, 50% of participants in the pooled experimental group and 50% in the pooled control group received standardised physical activity. Pooling was justified, as no interaction effect of physical activity was observed. Study authors stated: “Depending on the choice of outcome, two-armed full-scale trials may require fewer than 1000 participants (continuous outcome) or 2000 participants (categorical outcome)”. One SAE occurred, but the trial authors did not report in which trial arm	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	<b>Judgement:</b> method of random sequence generation not reported <b>Quote(s):</b> “following this, they were randomly assigned with equal probability among the four experimental conditions”
Allocation concealment (selection bias)	Unclear risk	<b>Judgement:</b> method of allocation concealment not reported <b>Quote(s):</b> “following this, they were randomly assigned with equal probability among the four experimental conditions”
Blinding of participants (performance bias)	High risk	<b>Judgement:</b> blinding not feasible
Blinding of personnel (performance bias)	High risk	<b>Judgement:</b> blinding not feasible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<b>Judgement:</b> study described as “single-blinded”, and at clinicaltrials.gov, it is explicitly described that outcome assessors were blinded



		<b>Quote(s):</b> “clinicaltrials.gov - Masking: Single Blind (Outcomes Assessor)”
Incomplete outcome data (attrition bias) All outcomes	Low risk	<b>Judgement:</b> for the outcome executive functioning: statistical analyses were reported to be done according to the intent-to-treat principle. Study authors described the analysis as being done according to the ITT principle, but we wonder if they referred only to the principle that the participant was analysed in the group to which he/she was randomised, regardless of cross-over. We are unsure if the 2 participants with missing data in the experimental group and the 1 in the control group were included in the analyses. We treated them as not analysed in our meta-analyses, in accordance with how the trial authors depicted their data in the tables
Selective reporting (reporting bias)	High risk	<b>Judgement:</b> all outcomes indicated in the methods section are adequately addressed in the results section, but at least 2 instruments (perceived cognitive functioning problems and quality of life) mentioned in NCT00688155 are not mentioned in the full publication
Other bias	High risk	<b>Judgement:</b> comparison 1: no other potential sources of bias detected; comparison 2: attendance rate in the combined CCI and physical activity group was statistically significantly better than in the physical activity only control group. The direction of bias would likely inflate CCI effects; we thus judged high risk of bias for comparison 2 <b>Quote(s):</b> “intervention attendance rates were higher in the CT and PACT groups: CT: 96%, PA: 76%, PACT: 90% (P = 0.004)”

Methods	<ul style="list-style-type: none"> <li>● <b>Design:</b> 2-arm RCT with parallel-group design</li> <li>● <b>Recruitment period:</b> not reported</li> <li>● <b>No. of centres involved:</b> 1</li> <li>● <b>Unit of randomisation:</b> individuals</li> <li>● <b>No. randomised:</b> not reported</li> <li>● <b>Number of arms considered in this review:</b> 2</li> <li>● <b>Maximum trial duration:</b> 3 months</li> <li>● <b>Funding by non-profit organisation:</b> this work was supported by Health and Health Services Research Fund (No. 09100911)</li> <li>● <b>Funding by commercial organisation:</b> none reported</li> <li>● <b>Publication status:</b> full-text report</li> </ul>
Participants	<ul style="list-style-type: none"> <li>● <b>Patient flow:</b> unclear number randomised; 109 described at baseline in experimental group; 100 described at baseline in control group</li> <li>● <b>Number of females:</b> 87 of 109 (80%) in experimental group 1; 77 of 100 (77%) in control group 1</li> <li>● <b>Average age (SD):</b> 70 (6.2) years in experimental group 1; 70 (6.6) years in control group 1</li> <li>● <b>Average (SD) education:</b> 8.71 (3.84) years in experimental group; 9.49 (4.44) years in control group</li> <li>● <b>Baseline cognitive function:</b> selection criteria on cognition in experimental group: right-handed community-dwelling Chinese older adults at risk of cognitive decline, as indicated by their Montreal Cognitive Assessment (MoCA) scores falling into the range of 19 to 26. MoCA, Hong Kong version, mean total score 23.6 (SD 1.88). Selection criteria on cognition in control group: right-handed community-dwelling Chinese older adults at risk of cognitive decline, as indicated by their MoCA scores falling into the range of 19 to 26. MoCA, Hong Kong version, mean total score 23.8 (SD 1.97)</li> <li>● <b>Ethnicity:</b> experimental group: white, Indian 109; Asian, Black, other unclear. Control group: white, Indian 100; Asian, Black, other unclear</li> <li>● <b>APOE:</b> number of participants positive for APOE not reported</li> </ul>
Interventions	<p><b>Type of experimental intervention:</b> computerised CT group; treatment duration 13 weeks; intervention provided in group format, under supervision</p> <ul style="list-style-type: none"> <li>● <b>Details of experimental intervention:</b> for both CT and AC groups, each participant was assigned a laptop, a headset, and a mouse, all of which were used for performing cognitive exercises. They used the same laptop for their entire training</li> <li>● <b>Type of concomitant treatment provided:</b> none reported</li> <li>● <b>Session duration:</b> 60 minutes in experimental group</li> <li>● <b>Number of treatment sessions:</b> 39 in experimental group</li> <li>● <b>Treatment frequency:</b> 3/week in experimental group</li> <li>● <b>Maximum treatment duration in weeks:</b> 13 in experimental group</li> </ul> <p><b>Type of control intervention:</b> other; treatment duration 13 weeks; intervention provided in group format, under supervision</p> <ul style="list-style-type: none"> <li>● <b>Details of control intervention:</b> participants in active control group “..were shown educational programs covering diverse topics (e.g., history, science, health information, and local social issues) on a group basis. Immediately after watching the video, they were instructed to answer several questions that were related to the video content”</li> </ul>

	<ul style="list-style-type: none"><li>● <b>Type of concomitant treatment provided:</b> none reported</li><li>● <b>Session duration:</b> 60 minutes in control group</li><li>● <b>Number of treatment sessions:</b> 39 in control group</li><li>● <b>Treatment frequency:</b> 3/week in control group</li><li>● <b>Maximum treatment duration in weeks:</b> 13 in control group</li></ul>	
Outcomes	<ul style="list-style-type: none"><li>● <b>Cognitive functioning outcomes considered</b><ul style="list-style-type: none"><li>○ Episodic memory measured with WMS-III Logical Memory Delayed recall at 3.25 months, on a scale from not reported to not reported with higher values indicating benefit*</li><li>○ Working memory measured with Digit Span, total at 3.25 months, on a scale from not reported to not reported with higher values indicating benefit</li></ul></li><li>● <b>Physical functioning outcome considered:</b> none reported</li><li>● <b>Quality of life outcome considered:</b> none reported</li><li>● <b>Safety outcome considered:</b> none reported</li><li>● <b>Depression outcome considered:</b> none reported</li><li>● <b>Other outcome data on cognitive functioning, not considered in our meta-analyses</b><ul style="list-style-type: none"><li>○ Episodic memory measured with WMS-III Logical Memory Immediate recall at 3.25 months, on a scale from not reported to not reported with higher values indicating benefit*</li><li>○ Episodic memory measured with WMS-III Family Pictures Delayed recall at 3.25 months, on a scale from not reported to not reported with higher values indicating benefit</li><li>○ Episodic memory measured with WMS-III Family Pictures Immediate recall at 3.25 months, on a scale from not reported to not reported with higher values indicating benefit</li><li>○ Working memory measured with Digit Vigilance Test at 3.25 months, on a scale from not reported to not reported with higher values indicating benefit</li><li>○ Working memory measured with Visual Spatial Span, total at 3.25 months, on a scale from not reported to not reported with higher values indicating benefit</li></ul></li></ul>	
Notes		
<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	<b>Judgement:</b> adequate random sequence generation <b>Quote(s):</b> “the 209 participants were randomly assigned to the CT and AC groups by an experimenter blind to the cognitive status of the participants using computer-generated random sequences of numbers”
Allocation concealment (selection bias)	Unclear risk	<b>Judgement:</b> the method of concealment is unclear as it is not understandable why participants had to be “rearranged”, and we

		<p>suspect that participants were not allocated consecutively, while it remains unclear if allocation of a participant could be foreseen by the researcher</p> <p><b>Quote(s):</b> “specifically, each participant ID was paired with a random number, and the order of the participants was rearranged based on the value of the assigned number (from smallest to largest)”</p>
Blinding of participants (performance bias)	High risk	<p><b>Judgement:</b> patients were not blinded to treatment</p>
Blinding of personnel (performance bias)	High risk	<p><b>Judgement:</b> research assistants could not be blinded, and they both supervised training and performed post-training assessments</p> <p><b>Quote(s):</b> “a research assistant was present in each training session to keep track of their attendance and address any questions pertaining to the task instruction raised by the participants. These research assistants were also responsible for conducting the post-training assessments”</p>
Blinding of outcome assessment (detection bias) All outcomes	High risk	<p><b>Judgement:</b> therapists, who could not be blinded, supervised training and perform post-training assessments</p> <p><b>Quote(s):</b> “a research assistant was present in each training session to keep track of their attendance and address any questions pertaining to the task instruction raised by the participants. These research assistants were also responsible for conducting the post-training assessments”</p>
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<p><b>Judgement:</b> reporting is inconclusive. Although according to the flow diagram it seems that 109 were randomised to experimental and 100 to control, we wonder if this merely reflects the number randomised who completed the follow-up assessment. There is no mention of intent-to-treat analyses, missing data, dropouts, or withdrawals, so that we judged risk as unclear</p> <p><b>Quote(s):</b> “our final sample consisted of 209 older adults (...) who successfully completed the pre- and post-training as-</p>

**Leung 2015** (Continued)

		essment, of which 109 older adults were randomly assigned to the CT group (...) and 100 older adults were in the AC group”
Selective reporting (reporting bias)	Low risk	<b>Judgement:</b> all outcomes described in the methods section are adequately addressed in the results section
Other bias	Unclear risk	<b>Judgment:</b> the selection process is not clear because study authors do not indicate the number of participants actually screened, those excluded, and reasons for exclusion. It is not clear whether inclusion was consecutive, and study authors mention that baseline characteristics were “matched”. With the latter, we assume they meant “comparable” <b>Quote(s):</b> “participants from the CT and AC groups were matched for their demographic characteristics”

**Peretz 2011**

Methods	<ul style="list-style-type: none"> <li>● <b>Design:</b> 2-arm RCT with factorial design</li> <li>● <b>Recruitment period:</b> not reported</li> <li>● <b>No. of centres involved:</b> 1</li> <li>● <b>Unit of randomisation:</b> individuals</li> <li>● <b>No. randomised:</b> 155</li> <li>● <b>Number of arms considered in this review:</b> 2</li> <li>● <b>Maximum trial duration:</b> 3 months</li> <li>● <b>Funding by non-profit organisation:</b> none reported</li> <li>● <b>Funding by commercial organisation:</b> NexSig Cognifit</li> <li>● <b>Publication status:</b> full-text report</li> </ul>
Participants	<ul style="list-style-type: none"> <li>● <b>Patient flow:</b> 84 randomised, 84 described at baseline in experimental group; 71 randomized, 71 described at baseline in control group</li> <li>● <b>Number of females:</b> 56 of 84 (67%) in experimental group 1; 40 of 71 (56%) in control group 1</li> <li>● <b>Average age (SD):</b> 68 (8.3) years in experimental group 1; 67 (7.2) years in control group 1</li> <li>● <b>Average (SD) education:</b> 14.6 (2.8) years in experimental group; 15.1 (3.6) years in control group</li> <li>● <b>Baseline cognitive function:</b> MMSE 29.0 (SD 1.2)</li> <li>● <b>Selection criteria on cognition overall:</b> healthy</li> <li>● <b>Ethnicity:</b> not reported</li> <li>● <b>APOE:</b> number of participants positive for APOE not reported</li> </ul>

Interventions	<p><b>Type of experimental intervention:</b> computerised CT, individualised; treatment duration of 12 weeks; intervention provided as individual training, without supervision</p> <ul style="list-style-type: none"> <li>● <b>Details of experimental intervention:</b> the personalised cognitive training programme selected for this study was the CogniFit Personal Coach. This programme's training regimen is based on the results of a baseline cognitive evaluation called the Neuropsychological Examination-CogniFit Personal Coach</li> <li>● <b>Session duration:</b> 20 to 30 minutes in experimental group</li> <li>● <b>Number of treatment sessions:</b> 36 in experimental group</li> <li>● <b>Treatment frequency:</b> 3/week in experimental group</li> <li>● <b>Maximum treatment duration in weeks:</b> 12 in experimental group</li> </ul> <p><b>Type of control intervention:</b> active computer; treatment duration of 12 weeks; intervention provided as individual training, without supervision</p> <ul style="list-style-type: none"> <li>● <b>Details of control intervention:</b> "twelve classic computer games that significantly engage cognitive processing were selected to create the computer games program. This program shared several features with the personalized cognitive training program, including the baseline cognitive evaluation, a total of 24 sessions comprising 3 different tasks, and a similar graphic design (Appendix 2). However, it did not have the adaptive training features of the personalized cognitive training program"</li> <li>● <b>Session duration:</b> 25 minutes in control group</li> <li>● <b>Number of treatment sessions:</b> 36 in control group</li> <li>● <b>Treatment frequency:</b> 3/week in control group</li> <li>● <b>Maximum treatment duration in weeks:</b> 12 in control group</li> </ul>
Outcomes	<ul style="list-style-type: none"> <li>● <b>Cognitive functioning outcomes considered</b> <ul style="list-style-type: none"> <li>○ Global cognitive functioning measured with Overall score: NexAde battery at 3 months, on a scale from not reported to not reported with higher values indicating benefit</li> <li>○ Episodic memory measured with Memory recall at 3 months, on a scale from not reported to not reported with higher values indicating benefit</li> <li>○ Executive functioning measured with Executive functions at 3 months, on a scale from not reported to not reported with higher values indicating benefit</li> <li>○ Working memory measured with Visuospatial working memory at 3 months, on a scale from not reported to not reported with higher values indicating benefit</li> </ul> </li> <li>● <b>Physical functioning outcome considered:</b> none reported</li> <li>● <b>Quality of life outcome considered:</b> none reported</li> <li>● <b>Safety outcome considered:</b> none reported</li> <li>● <b>Depression outcome considered:</b> none reported</li> <li>● <b>Other outcome data on cognitive functioning, not considered in our meta-analyses</b> <ul style="list-style-type: none"> <li>○ Episodic memory measured with Memory recognition at 3 months, on a scale from not reported to not reported with higher values indicating benefit</li> <li>○ Episodic memory measured with Visuospatial learning at 3 months, on a scale from not reported to not reported with higher values indicating benefit</li> <li>○ Executive functioning measured with Focused attention at 3 months, on a scale from not reported to not reported with higher values indicating benefit</li> <li>○ Executive functioning measured with Mental flexibility at 3 months, on a scale from not reported to not reported with higher values indicating benefit</li> <li>○ Working memory measured with Sustained attention at 3 months, on a scale from not reported to not reported with higher values indicating benefit</li> </ul> </li> </ul>

Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<b>Judgement:</b> adequate random sequence generation <b>Quote(s):</b> "random number generator"
Allocation concealment (selection bias)	Low risk	<b>Judgement:</b> adequate method of allocation concealment <b>Quote(s):</b> "encrypted codes"
Blinding of participants (performance bias)	High risk	<b>Judgement:</b> a large number of participants correctly identified their group assignment; this is assumed to be an indication of poor blinding of participants <b>Quote(s):</b> "...with investigators and participants being blind to group assignment. Participants received a CD containing either the cognitive training program or the computer games program. To preserve blindness, all CDs were labelled and packaged identically, and all graphics, fonts, opening screens, baseline evaluations and post-training evaluations were identical on both CDs. Personnel were kept unaware of the participants' group assignment, which was encrypted in the code number labels on the CDs"; "Thirty-six percent of the subjects correctly identified their group assignment (21% personalized cognitive training, 15% games)"
Blinding of personnel (performance bias)	Low risk	<b>Judgement:</b> adequate method of therapist blinding <b>Quote(s):</b> "...with investigators and participants being blind to group assignment. Participants received a CD containing either the cognitive training program or the computer games program. To preserve blindness, all CDs were labelled and packaged identically, and all graphics, fonts, opening screens, baseline evaluations and post-training evaluations were identical on both CDs. Personnel were kept unaware of the participants' group assignment, which was

		encrypted in the code number labels on the CDs"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<b>Judgement:</b> not clearly reported if outcome assessors were blinded, but all personnel were likely kept blinded to treatment assignment <b>Quote(s):</b> "personnel were kept unaware of the participants' group assignment, which was encrypted in the code number labels on the CDs"
Incomplete outcome data (attrition bias) All outcomes	High risk	<b>Judgement:</b> for the outcome episodic memory, 66 out of 84 (79%) randomised were analysed in experimental group, and 55 out of 71 (77%) randomised were analysed in control group. Statistical analyses were reported to be done according to the intent-to-treat principle. Although study authors state that they used an ITT, 18 participants in experimental group and 16 in control group did not complete the training and had no data available at baseline, follow-up, or both <b>Quote(s):</b> "a total of 34 (22%) participants (18 in the cognitive training group and 16 in the computer games group) did not complete the training; the majority of those (n = 29) never began the home training"
Selective reporting (reporting bias)	Low risk	<b>Judgement:</b> all outcomes indicated in the methods section are reported in the results section
Other bias	Low risk	<b>Judgement:</b> no other apparent risks of bias



Methods	<ul style="list-style-type: none"> <li>• <b>Design:</b> 4-arm RCT with parallel-group design</li> <li>• <b>Recruitment period:</b> not reported</li> <li>• <b>No. of centres involved:</b> 1</li> <li>• <b>Unit of randomisation:</b> individuals</li> <li>• <b>No. randomised:</b> 180</li> <li>• <b>Number of arms considered in this review:</b> 4</li> <li>• <b>Maximum trial duration:</b> 4 months</li> <li>• <b>Funding by non-profit organisation:</b> Beckman Insititute</li> <li>• <b>Funding by commercial organisation:</b> none reported</li> <li>• <b>Publication status:</b> full-text report</li> </ul>
Participants	<ul style="list-style-type: none"> <li>• <b>Patient flow:</b> 45 randomised, 33 described at baseline in experimental group 1; 48 randomised, 29 described at baseline in experimental group 2; 45 randomised, 31 described at baseline in experimental group 3; 42 randomised, 29 described at baseline in control group</li> <li>• <b>Number of females:</b> 23 of 33 (70%) in experimental group 1; 20 of 29 (69%) in experimental group 2; 22 of 31 (71%) in experimental group 3; 19 of 29 (66%) in control group 1</li> <li>• <b>Average age (SD):</b> 80 (5.4) years in experimental group 1; 79 (5.5) years in experimental group 2; 79 (5.8) years in experimental group 3; 81 (5.3) years in control group 1</li> <li>• <b>Average (SD) education:</b> experimental group 1: some college and above: 26 (78, 8%); experimental group 2: some college and above: 17 (58,6%); experimental group 3: some college and above: 28 (90,3%); control group 1: some college and above: 23 (79,3%)</li> <li>• <b>Baseline cognitive function:</b> MMSE &gt; 24</li> <li>• <b>Selection criteria on cognition overall:</b> healthy</li> <li>• <b>Ethnicity:</b> not reported</li> <li>• <b>APOE:</b> number of participants positive for APOE not reported</li> </ul>
Interventions	<p><b>Type of experimental intervention 1:</b> computerised CT group; treatment duration of 16 weeks; intervention provided in group format, under supervision</p> <ul style="list-style-type: none"> <li>• <b>Details of experimental intervention:</b> Cognifit</li> <li>• <b>Session duration:</b> 40 minutes in experimental group</li> <li>• <b>Number of treatment sessions:</b> 48 in experimental group</li> <li>• <b>Treatment frequency:</b> 3/week in experimental group</li> <li>• <b>Maximum treatment duration in weeks:</b> 16 in experimental group</li> </ul> <p><b>Type of experimental intervention 2:</b> mixed</p> <ul style="list-style-type: none"> <li>• <b>Details of experimental intervention 2:</b> cognitive training as for experimental arm 1 in combination with group-based supervised physical training, which consisted of 3 weekly 45-minute sessions, with at least a 1-day interval between training days, during 16 weeks</li> <li>• <b>Session duration:</b> 40 minutes in experimental group 2</li> <li>• <b>Number of treatment sessions:</b> 48 in experimental group 2</li> <li>• <b>Treatment frequency:</b> 3/week in experimental group 2</li> <li>• <b>Maximum treatment duration in weeks:</b> 16 in experimental group 2</li> </ul> <p><b>Type of control intervention 1:</b> other; treatment duration of 16 weeks; intervention provided in group format, under supervision</p> <ul style="list-style-type: none"> <li>• <b>Details of control intervention:</b> this group was assigned selected book excerpts</li> </ul>

	to be read at home and held one 60-minute weekly meeting during which the best ways to achieve the goals advocated in the book were discussed. This group was classified as an active control group because it was compared with the Cognifit group <ul style="list-style-type: none"><li>● <b>Session duration:</b> 60 minutes in control group</li><li>● <b>Number of treatment sessions:</b> 16 in control group</li><li>● <b>Treatment frequency:</b> 1/week in control group</li><li>● <b>Maximum treatment duration:</b> 16 in control group</li></ul> <b>Type of control intervention 2:</b> other; intervention provided in group format, under supervision <ul style="list-style-type: none"><li>● <b>Details of control intervention 2:</b> group-based supervised physical training.</li></ul> This group was classified as an inactive control group because it was compared with the mixed experimental intervention <ul style="list-style-type: none"><li>● <b>Session duration:</b> 45 minutes in control group 2</li><li>● <b>Number of treatment sessions:</b> 48 in control group 2</li><li>● <b>Treatment frequency:</b> 3/week in control group 2</li><li>● <b>Maximum treatment duration in weeks:</b> 16 in control group 2</li></ul>	
Outcomes	<ul style="list-style-type: none"><li>● <b>Cognitive functioning outcomes considered for both comparisons</b><ul style="list-style-type: none"><li>○ Speed of processing measured with SVP at 4 months, on a scale from not reported to not reported with higher values indicating benefit</li><li>○ Working memory measured with AM Cognifit at 4 months, on a scale from not reported to not reported with higher values indicating benefit</li></ul></li><li>● <b>Physical functioning outcome considered:</b> none reported</li><li>● <b>Quality of life outcome considered:</b> none reported</li><li>● <b>Safety outcome considered:</b> none reported</li><li>● <b>Depression outcome considered:</b> none reported</li><li>● <b>Other outcome data on cognitive functioning, not considered in our meta-analyses</b><ul style="list-style-type: none"><li>○ Cognitif subtests</li></ul></li></ul>	
Notes		
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<b>Judgement:</b> method of random sequence generation not reported <b>Quote(s):</b> “following the screening subjects were randomized to the four intervention groups”
Allocation concealment (selection bias)	Unclear risk	<b>Judgement:</b> method of allocation concealment not reported <b>Quote(s):</b> “following the screening subjects were randomized to the four intervention groups”
Blinding of participants (performance bias)	Unclear risk	<b>Judgement:</b> no information reported

**Shatil 2013** (Continued)

Blinding of personnel (performance bias)	Unclear risk	<b>Judgement:</b> no information reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<b>Judgement:</b> blinding of outcome assessment not reported <b>Quote(s):</b> “to measure change in cognitive function following the interventions, we used the CogniFit neuropsychological evaluation”
Incomplete outcome data (attrition bias) All outcomes	High risk	<b>Judgement:</b> 62 out of 93 (67%) randomised were analysed in experimental group, and 60 out of 87 (69%) randomised were analysed in control group <b>Quotes:</b> “55 participants (30.5%) left during the baseline testing period, while another battery of tests (to be reported elsewhere) were being administered; before the training interventions..”; “three participants, two in the Cognitive Training Group and one in the Physical Activity Group, left the study, due to health problems. Thus, altogether, 58 subjects (32.2% among the 180 enlisted study participants) withdrew from the study and 122 adhered to it”
Selective reporting (reporting bias)	Low risk	<b>Judgement:</b> all outcomes indicated in the methods section are reported in the results section
Other bias	High risk	<b>Judgement:</b> potential high risk of bias because the main author (Shatil) is an employee of the CogniFit Company

**van het Reve 2014**

Methods	<ul style="list-style-type: none"> <li>• <b>Design:</b> international multi-centre 2-arm RCT with parallel-group design</li> <li>• <b>Recruitment period:</b> 2011 to 2013</li> <li>• <b>No. of centres involved:</b> 14</li> <li>• <b>Unit of randomisation:</b> individuals</li> <li>• <b>No. randomised:</b> 182</li> <li>• <b>Number of arms considered in this review:</b> 2</li> <li>• <b>Maximum trial duration:</b> 3 months</li> <li>• <b>Funding by non-profit organisation:</b> none reported</li> <li>• <b>Funding by commercial organisation:</b> none reported</li> <li>• <b>Publication status:</b> full-text report</li> </ul>
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Participants	<ul style="list-style-type: none"> <li>● <b>Patient flow:</b> 84 randomised, 69 described at baseline in experimental group; 98 randomised, 76 described at baseline in control group</li> <li>● <b>Number of females:</b> 49 of 69 (71%) in experimental group 1; 52 of 76 (68%) in control group 1</li> <li>● <b>Average age (SD):</b> 81 (8.3) years in experimental group 1; 82 (6.3) years in control group</li> <li>● <b>Education:</b> experimental group 1: university/college 7 (10), vocational education 41 (59), no educated profession 21 (30), in a sitting position past profession 18 (26); control 1: university/college 4 (5), vocational education 52 (68), no educated profession 20 (26), in a sitting position past profession 15 (20)</li> <li>● <b>Baseline cognitive function:</b> selection criteria on cognition overall: healthy</li> <li>● <b>Selection criteria on cognition:</b> experimental group: MMSE score (mean <math>\pm</math> SD): 27.6 <math>\pm</math> 2.6; control group: MMSE score (mean <math>\pm</math> SD): 27.7 <math>\pm</math> 2.9</li> <li>● <b>Ethnicity:</b> not reported</li> <li>● <b>APOE:</b> number of participants positive for APOE not reported*</li> </ul>
Interventions	<p><b>Type of experimental intervention:</b> computerised CT group; treatment duration of 12 weeks; intervention provided in group format, under supervision</p> <ul style="list-style-type: none"> <li>● <b>Details of experimental intervention:</b> cognitive training, with the CogniPlus training programme</li> <li>● <b>Type of concomitant treatment provided:</b> strength-balance training</li> <li>● <b>Session duration:</b> 10 minutes in experimental group</li> <li>● <b>Number of treatment sessions:</b> 36 in experimental group</li> <li>● <b>Treatment frequency:</b> 3/week in experimental group</li> <li>● <b>Maximum treatment duration in weeks:</b> 12 in experimental group</li> </ul> <p><b>Type of control intervention:</b> other; treatment duration of 12 weeks; intervention provided in group format, under supervision</p> <ul style="list-style-type: none"> <li>● <b>Details of control intervention:</b> exercise programme consisted of twice-weekly 30-minute progressive resistance training on age-adapted machines and 10-minute balance training during 12 weeks</li> <li>● <b>Type of concomitant treatment provided:</b> strength-balance training</li> <li>● <b>Session duration:</b> 40 minutes in control group</li> <li>● <b>Number of treatment sessions:</b> 24 in control group</li> <li>● <b>Treatment frequency:</b> 2/week in control group</li> <li>● <b>Maximum treatment duration in weeks:</b> 12 in control group</li> </ul>
Outcomes	<ul style="list-style-type: none"> <li>● <b>Cognitive functioning outcomes considered</b> <ul style="list-style-type: none"> <li>○ Executive functioning measured with TMT-B at 3 months, on a scale from not reported to not reported with lower values indicating benefit</li> <li>○ Speed of processing measured with TMT-A at 3 months, on a scale from not reported to not reported with lower values indicating benefit</li> </ul> </li> <li>● <b>Physical functioning outcome considered:</b> none reported</li> <li>● <b>Quality of life outcome considered:</b> none reported</li> <li>● <b>Safety outcome considered:</b> none reported</li> <li>● <b>Depression outcome considered:</b> none reported</li> </ul>
Notes	<p>Due to strength-balance training, which was given to both groups, we included the study in the inactive control comparison</p>

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<b>Judgement:</b> adequate random sequence generation <b>Quote(s):</b> "to ensure allocation concealment, participants in each home were enrolled by the health care staff, and randomized by the person assessing the outcome measures using simple (unrestricted) randomisation.. based on a table of random numbers"
Allocation concealment (selection bias)	Unclear risk	<b>Judgement:</b> unclear allocation concealment <b>Quote(s):</b> "the assessor generated an unpredictable allocation sequence, which was concealed until assignment occurred. Each participant in every home received a two digit number (01, 02, 03, ...) resulting in a rank order of the participants. With the help of the random numbers table the assessor decided a priori to pick a number from the table with a pencil and go through the table either from bottom-right to upper-left in a diagonal way, horizontally from left-to-right or right-to-left, etc"
Blinding of participants (performance bias)	Unclear risk	<b>Judgement:</b> patient blinding was not reported, but it is unlikely <b>Quote(s):</b> "blinding of the investigator was not possible because the investigator conducted part of the assessments"
Blinding of personnel (performance bias)	High risk	<b>Judgement:</b> investigators were not blinded <b>Quote(s):</b> "blinding of the investigator was not possible because the investigator conducted part of the assessments"
Blinding of outcome assessment (detection bias) All outcomes	High risk	<b>Judgement:</b> outcome assessment was not blinded <b>Quote(s):</b> "blinding of the investigator was not possible because the investigator conducted part of the assessments"
Incomplete outcome data (attrition bias) All outcomes	High risk	<b>Judgement:</b> 69 out of 84 (82%) randomised were analysed in the experimental

		group, and 76 out of 98 (78%) randomised were analysed in the control group, although statistical analyses were reported to be done according to the intent-to-treat principle. In addition, 4 participants were re-assigned by investigators to the control group despite being initially randomised to the intervention group <b>Quote(s):</b> “a total of 156 participants completed the intervention (137 subjects living in the homes-for-the-aged and 19 subjects living in the vicinity) resulting in 14.3% attrition”; “Four participants that were not able to conduct the cognitive training due to vision problems were manually allocated to the SB group after randomization. Thus, we reported 98 participants in SB and 84 participants in SBC after this adaptation”
Selective reporting (reporting bias)	Low risk	<b>Judgement:</b> all outcomes indicated in the methods section are reported in the results section
Other bias	Low risk	<b>Judgement:</b> no other sources of bias detected <b>Quote(s):</b> none

AC: active control.

AE: adverse event.

APOE: apolipoprotein E.

AR: aerobics and resistance.

BDT-DT: The Baddeley Dual Task

CCI: computerised cognitive intervention.

COWAT: Controlled Oral Word Association Test.

CT: computed tomography.

CWIT: Color-Word Interference Test.

DT: dual task.

FCSRT: Free and Cued Selective Reminding Test.

GDS-Sf: short-form Geriatric Depression Scale.

HVLT: Hopkins Verbal Learning Test.

ITT: intention-to-treat.

MMRM: mixed model for repeated measures.

MMSE: Mini Mental State Examination.

MoCA: Montreal Cognitive Assessment.

RBMT: Rivermead Behavioural Memory Test.

RCT: randomised controlled trial.

RT: Reaction time.

SAE: serious adverse event.

SD: standard deviation.  
 ST: stretching and toning.  
 SVP: speed of visual information processing.  
 TMT: Trail Making Test.  
 WMS-III: Wechsler Memory Scale, Third Edition.

### Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
<a href="#">Adel 2013</a>	Wrong study design
<a href="#">Alves 2014</a>	Wrong intervention
<a href="#">Alves 2014a</a>	Wrong intervention
<a href="#">Anderson 2014</a>	Intervention shorter than 12 weeks
<a href="#">Ann 2012</a>	Wrong patient population
<a href="#">Anon 2007</a>	Nature of intervention unclear
<a href="#">Anon 2007a</a>	Nature of intervention unclear
<a href="#">Apostolo 2014</a>	Wrong patient population
<a href="#">Baglio 2011</a>	Nature of intervention unclear
<a href="#">Ball 2002</a>	Intervention shorter than 12 weeks
<a href="#">Ball 2002a</a>	Duplicate
<a href="#">Ball 2006</a>	Intervention shorter than 12 weeks
<a href="#">Ball 2013</a>	Intervention shorter than 12 weeks
<a href="#">Ballesteros 2014</a>	Duplicate
<a href="#">Ballesteros 2014a</a>	Duplicate
<a href="#">Ballesteros 2015</a>	Duplicate
<a href="#">Ballesteros 2015a</a>	Duplicate
<a href="#">Ballesteros 2017</a>	Intervention shorter than 12 weeks
<a href="#">Bamidis 2015</a>	Wrong study design

(Continued)

Baniqued 2014	Adult population
Baniqued 2015	Younger than 30 years of age
Barban 2012	Duplicate
Barban 2016	Wrong study design
Barbosa 2015	Wrong intervention
Barcelos 2015	Wrong intervention
Barnes 2006	Intervention shorter than 12 weeks
Barnes 2009	Duplicate
Barnes 2013	Wrong patient population
Basak 2016	Intervention shorter than 12 weeks
Beck 2013	Wrong intervention
Belchior 2007	Wrong outcomes
Belchior 2008	Wrong outcomes
Belleville 2006	Wrong intervention
Belleville 2014	Wrong outcomes
Berry 2010	Intervention shorter than 12 weeks
Bier 2015	Wrong study design
Binder 2016	Intervention shorter than 12 weeks
Bittner 2013	Wrong study design
Borella 2010	Intervention shorter than 12 weeks
Borella 2013	Wrong intervention
Borella 2014	Duplicate
Borella 2017	Wrong intervention
Boripuntakul 2012	Wrong intervention



(Continued)

Borress 2013	Wrong patient population
Bottiroli 2009	Duplicate
Bottiroli 2009a	Intervention shorter than 12 weeks
Bozoki 2013	Intervention shorter than 12 weeks
Brehmer 2012	Intervention shorter than 12 weeks
Brum 2013	Duplicate
Buitenweg 2017	Wrong intervention
Buiza 2008	Wrong intervention
Bureš 2016	Intervention shorter than 12 weeks
Buschert 2011	Wrong intervention
Buschert 2011a	Duplicate
Buschert 2012	Wrong intervention
Buschert 2012a	Duplicate
Calkins 2011	Wrong intervention
Cammarata 2011	No outcome given
Cancela 2015	Wrong patient population
Candela 2015	Wrong intervention
Cantarella 2017	Intervention shorter than 12 weeks
Cao 2016	Wrong route of administration
Carretti 2013	Wrong intervention
Casutt 2014	Wrong outcomes
Chapman 2015	Wrong intervention
Chapman 2016	Wrong intervention
Chapman 2017	Wrong intervention

(Continued)

Cheng 2012	Wrong intervention
Cheng 2018	Wrong patient population
Cho 2002	Younger than 30 years of age
Cleverley 2012	Wrong intervention
Cohen-Mansfield 2014	Wrong intervention
Cohen-Mansfield 2014a	Wrong intervention
Cohen-Mansfield 2015	Wrong intervention
Cohen-Mansfield 2015a	Duplicate
Combourieu 2014	Wrong outcomes
Corbett 2015	Wrong patient population
Costa 2015	Wrong patient population
Danassi 2015	Duplicate
Dannhauser 2014	Wrong study design
de Almondes 2017	Intervention shorter than 12 weeks
de Macedo 2015	Wrong outcomes
De Vreesse 1996	Wrong intervention
Diamond 2015	Intervention shorter than 12 weeks
Dittmann-Kohli 1991	Wrong intervention
Djabelkhir 2017	Wrong patient population
Duncan 2009	Wrong intervention
Dwolatzy 2005	Intervention shorter than 12 weeks
Eckroth-Bucher 2009	Wrong patient population
Edwards 2005	Intervention shorter than 12 weeks
Edwards 2011	Intervention shorter than 12 weeks

(Continued)

Edwards 2015	Intervention shorter than 12 weeks
Edwards 2015a	Intervention shorter than 12 weeks
Efthymiou 2011	Wrong comparator
Engvig 2014	Wrong study design
Fabre 2002	Wrong intervention
Faille 2007	Nature of intervention unclear
Fairchild 2010	Wrong intervention
Feng 2013	Wrong intervention
Feng 2015	Wrong intervention
Feng 2017	Wrong patient population
Fiatarone Singh 2014	Wrong patient population
Finn 2011	Intervention shorter than 12 weeks
Finn 2015	Intervention shorter than 12 weeks
Finn 2015a	Duplicate
Flak 2013	Study protocol
Flak 2014	Study protocol
Flak 2014a	Study protocol
Flak 2016	Study protocol
Foerster 2009	No outcome given
Forloni 2012	No outcome given
Forster 2011	Wrong intervention
Fortman 2013	Wrong comparator
Gagnon 2012	Wrong study design
Gagnon 2012a	Intervention shorter than 12 weeks

(Continued)

Gaitan 2013	Wrong patient population
Gajewski 2012	Intervention shorter than 12 weeks
Gajewski 2017	Intervention shorter than 12 weeks
Garcia-Campuzano 2013	Nature of intervention unclear
Gates 2011	Study protocol
Gill 2016	Wrong intervention
Gillette 2009	No outcome given
Giovannini 2015	No outcome given
Giuli 2016	Wrong intervention
Giuli 2017	Wrong intervention
Golino 2017	Wrong intervention
Gooding 2016	Wrong patient population
Haesner 2015	Wrong study design
Haesner 2015a	Intervention shorter than 12 weeks
Haimov 2013	Intervention shorter than 12 weeks
Haimov 2013a	Intervention shorter than 12 weeks
Haimov 2013b	Intervention shorter than 12 weeks
Haimov 2013c	Duplicate
Haimov 2013d	Intervention shorter than 12 weeks
Haimov 2014	Intervention shorter than 12 weeks
Haimov 2014a	Intervention shorter than 12 weeks
Hardy 2015	Intervention shorter than 12 weeks
Hausmann 2012	Wrong intervention
Hayashi 2012	Wrong intervention

(Continued)

<a href="#">Hayslip B Jr 2016</a>	Intervention shorter than 12 weeks
<a href="#">Heinzel 2014</a>	Intervention shorter than 12 weeks
<a href="#">Herrera 2012</a>	Wrong patient population
<a href="#">Hudak 2013</a>	Intervention shorter than 12 weeks
<a href="#">Hötting 2013</a>	Intervention shorter than 12 weeks
<a href="#">Ignjatovic 2015</a>	Younger than 30 years of age
<a href="#">Irigaray 2012</a>	Wrong intervention
<a href="#">Israel 1997</a>	Nature of intervention unclear
<a href="#">ISRCTN70130279</a>	Wrong intervention
<a href="#">Jackson 2012</a>	Nature of intervention unclear
<a href="#">Jansen 2012</a>	Wrong intervention
<a href="#">Jean 2010</a>	Intervention shorter than 12 weeks
<a href="#">Jeong 2016</a>	Wrong intervention
<a href="#">Jobe 2001</a>	Intervention shorter than 12 weeks
<a href="#">Jones 2013</a>	Intervention shorter than 12 weeks
<a href="#">Kampanaros 2010</a>	Wrong intervention
<a href="#">Kholin 2010</a>	Intervention shorter than 12 weeks
<a href="#">Kim 2012</a>	Wrong outcomes
<a href="#">Kim 2013</a>	Intervention shorter than 12 weeks
<a href="#">Kim 2013a</a>	Wrong outcomes
<a href="#">Kim 2015</a>	Intervention shorter than 12 weeks
<a href="#">Kim 2015a</a>	Intervention shorter than 12 weeks
<a href="#">Kim 2015b</a>	Duplicate
<a href="#">Kivipelto 2014</a>	Wrong intervention

(Continued)

<a href="#">Klusmann 2009</a>	Duplicate
<a href="#">Klusmann 2010a</a>	Duplicate
<a href="#">Klusmann 2011</a>	Younger than 30 years of age
<a href="#">Kudelka 2014</a>	Intervention shorter than 12 weeks
<a href="#">Kwak 2015</a>	Nature of intervention unclear
<a href="#">Kwak 2017</a>	Nature of intervention unclear
<a href="#">Kwok 2013</a>	Intervention shorter than 12 weeks
<a href="#">Kwok 2013a</a>	Wrong patient population
<a href="#">Lampit 2013</a>	Wrong study design
<a href="#">Lavretsky 2016</a>	Nature of intervention unclear
<a href="#">Law 2014</a>	Intervention shorter than 12 weeks
<a href="#">Law 2014a</a>	Duplicate
<a href="#">Lee 2013</a>	Intervention shorter than 12 weeks
<a href="#">Lee 2013a</a>	Intervention shorter than 12 weeks
<a href="#">Lee 2013b</a>	Intervention shorter than 12 weeks
<a href="#">Lee 2014</a>	Intervention shorter than 12 weeks
<a href="#">Lee 2015</a>	Intervention shorter than 12 weeks
<a href="#">León 2015</a>	Wrong comparator
<a href="#">Li 2010</a>	Intervention shorter than 12 weeks
<a href="#">Linde 2014</a>	Nature of intervention unclear
<a href="#">Mace 2015</a>	Intervention shorter than 12 weeks
<a href="#">Mahncke 2006</a>	Intervention shorter than 12 weeks
<a href="#">Man 2012</a>	Wrong comparator
<a href="#">Mann 2012</a>	Wrong patient population
<a href="#">Margrett 2006</a>	Wrong patient population

(Continued)

Mayas 2014	Intervention shorter than 12 weeks
McAvinue 2013	Intervention shorter than 12 weeks
McDaniel 2014	Intervention shorter than 12 weeks
McDougall 2012	Intervention shorter than 12 weeks
Middleton 2012	Wrong intervention
Miller 2013	Intervention shorter than 12 weeks
Mohs 1998	Wrong intervention
Mombelli 2012	No outcome given
Moon 2013	Intervention shorter than 12 weeks
Mowszowski 2014	Intervention shorter than 12 weeks
Mowszowski 2014a	Duplicate
Mozolic 2010	Intervention shorter than 12 weeks
Mozolic 2011	Intervention shorter than 12 weeks
Muller 2011	Nature of intervention unclear
Na 2013	Duplicate
Na 2014	Nature of intervention unclear
Naismith 2014	Duplicate
Navarro 2006	Intervention shorter than 12 weeks
NCT02417558 2015	Nature of intervention unclear
NCT02462135 2014	No outcome given
NCT02480738 2012	No outcome given
NCT02512627 2015	No outcome given
NCT02747784 2016	Wrong patient population
NCT02774083 2015	Wrong comparator

(Continued)

<a href="#">NCT02785315 2016</a>	Wrong intervention
<a href="#">NCT02808676 2016</a>	Wrong intervention
<a href="#">Neely 2013</a>	Nature of intervention unclear
<a href="#">Ng 2015</a>	Wrong intervention
<a href="#">Ngandu 2015</a>	Wrong intervention
<a href="#">Ngandu 2015a</a>	Wrong intervention
<a href="#">Nishiguchi 2015</a>	Wrong intervention
<a href="#">Nouchi 2012</a>	Intervention shorter than 12 weeks
<a href="#">Nouchi 2013</a>	Intervention shorter than 12 weeks
<a href="#">Nozawa 2015</a>	Intervention shorter than 12 weeks
<a href="#">O’Caoimh 2015</a>	Intervention shorter than 12 weeks
<a href="#">Oei 2013</a>	Intervention shorter than 12 weeks
<a href="#">Oliveira 2013</a>	Intervention shorter than 12 weeks
<a href="#">Optale 2010</a>	Wrong patient population
<a href="#">Otsuka 2015</a>	Wrong study design
<a href="#">Park 2009</a>	Nature of intervention unclear
<a href="#">Park 2014</a>	Intervention shorter than 12 weeks
<a href="#">Payne 2012</a>	Wrong intervention
<a href="#">Payne 2017</a>	Intervention shorter than 12 weeks
<a href="#">Rahe 2015</a>	Intervention shorter than 12 weeks
<a href="#">Rahe 2015a</a>	Intervention shorter than 12 weeks
<a href="#">Rebok 2013</a>	Intervention shorter than 12 weeks
<a href="#">Rebok 2014</a>	Intervention shorter than 12 weeks
<a href="#">Redick 2013</a>	Younger than 30 years of age



(Continued)

<a href="#">Requena 2016</a>	Wrong intervention
<a href="#">Rizkalla 2015</a>	Intervention shorter than 12 weeks
<a href="#">Rojas 2013</a>	Wrong intervention
<a href="#">Rose 2015</a>	Intervention shorter than 12 weeks
<a href="#">Rosen 2011</a>	Intervention shorter than 12 weeks
<a href="#">Rozzini 2007</a>	Wrong patient population
<a href="#">Ryu 2013</a>	Wrong study design
<a href="#">Sakka 2015</a>	Wrong study design
<a href="#">Santos 2011</a>	Wrong comparator
<a href="#">Schoene 2015</a>	Duplicate
<a href="#">Schoene 2015a</a>	Duplicate
<a href="#">Schumacher 2013</a>	Intervention shorter than 12 weeks
<a href="#">Shah 2012</a>	Wrong patient population
<a href="#">Shatil 2014</a>	Intervention shorter than 12 weeks
<a href="#">Shatil 2014a</a>	Duplicate
<a href="#">Sisco 2013</a>	Intervention shorter than 12 weeks
<a href="#">Slegers 2009</a>	Wrong intervention
<a href="#">Smith 2009</a>	Intervention shorter than 12 weeks
<a href="#">Smith-Ray 2014</a>	Intervention shorter than 12 weeks
<a href="#">Smith-Ray 2015</a>	Intervention shorter than 12 weeks
<a href="#">Smith-Ray 2015a</a>	Duplicate
<a href="#">Solomon 2014</a>	Wrong comparator
<a href="#">Song 2009</a>	Wrong intervention
<a href="#">Stepankova 2014</a>	Intervention shorter than 12 weeks

(Continued)

Stine-Morrow 2014	Intervention shorter than 12 weeks
Strenziok 2013	Duplicate
Strenziok 2014	Intervention shorter than 12 weeks
Sturz 2011	Wrong patient population
Sturz 2011a	Nature of intervention unclear
Sturz 2015	Duplicate
Styliadis 2015	Intervention shorter than 12 weeks
Styliadis 2015a	Duplicate
Suo 2012	Wrong outcomes
Szelag 2012	Intervention shorter than 12 weeks
Talib 2008	Intervention shorter than 12 weeks
Tappen 2014	Wrong intervention
Tennstedt 2013	Study protocol
Tesky 2012	Wrong intervention
Tsai 2008	Wrong study design
Tsolaki 2013	Nature of intervention unclear
Tucker-Drob 2009	Wrong study design
van den Berg 2016	Intervention shorter than 12 weeks
van der Ploeg 2016	Wrong study design
Vance 2007	Intervention shorter than 12 weeks
Vidovich 2009	Intervention shorter than 12 weeks
Vidovich 2015	Intervention shorter than 12 weeks
Vidovich 2015a	Duplicate
von Bastian 2013	Intervention shorter than 12 weeks

(Continued)

Wadley 2007	Wrong study design
Walton 2015	Intervention shorter than 12 weeks
Wang 2013	Wrong intervention
Weicker 2013	Intervention shorter than 12 weeks
Wild-Wall 2012	Wrong outcomes
Williams 2014	Intervention shorter than 12 weeks
Willis 1986	Intervention shorter than 12 weeks
Willis 2006	Intervention shorter than 12 weeks
Willis 2006a	Duplicate
Willis 2007	Duplicate
Willis 2013	Intervention shorter than 12 weeks
Wojtynska 2011	Intervention shorter than 12 weeks
Wolinsky 2006	Intervention shorter than 12 weeks
Wolinsky 2006a	Intervention shorter than 12 weeks
Wolinsky 2010	Intervention shorter than 12 weeks
Wolinsky 2010a	Intervention shorter than 12 weeks
Wolinsky 2013	Intervention shorter than 12 weeks
Wolinsky 2015	Intervention shorter than 12 weeks
Yam 2014	Wrong intervention
Yassuda 2015	Intervention shorter than 12 weeks
Yip 2012	Intervention shorter than 12 weeks
Yoonmi 2012	Intervention shorter than 12 weeks
Youn 2011	Intervention shorter than 12 weeks
Zelinski 2011	Wrong study design

(Continued)

<a href="#">Zelinski 2011a</a>	Intervention shorter than 12 weeks
<a href="#">Zhuang 2013</a>	Wrong patient population
<a href="#">Zimmermann 2014</a>	Intervention shorter than 12 weeks

## DATA AND ANALYSES

### Comparison 1. Computerised cognition-based training versus active control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global cognitive function	2		Std. Mean Difference (Random, 95% CI)	Subtotals only
1.1 End of trial	2	198	Std. Mean Difference (Random, 95% CI)	-1.06 [-2.73, 0.61]
1.2 Immediate time point (12 weeks)	2	198	Std. Mean Difference (Random, 95% CI)	-1.12 [-2.67, 0.43]
1.3 Medium time point (1 year to 2 years)	1	77	Std. Mean Difference (Random, 95% CI)	-0.21 [-0.66, 0.24]
2 Episodic memory	4		Std. Mean Difference (Random, 95% CI)	Subtotals only
2.1 End of trial at Immediate time point (12 weeks)	4	439	Std. Mean Difference (Random, 95% CI)	-0.18 [-1.00, 0.64]
3 Speed of processing	2		Std. Mean Difference (Random, 95% CI)	Subtotals only
3.1 End of trial at immediate time point (12 weeks)	2	138	Std. Mean Difference (Random, 95% CI)	-0.63 [-1.14, -0.12]
4 Executive function	3		Std. Mean Difference (Random, 95% CI)	Subtotals only
4.1 End of trial at immediate time point (12 weeks)	3	230	Std. Mean Difference (Random, 95% CI)	-0.34 [-1.45, 0.77]
5 Working memory	3		Std. Mean Difference (Random, 95% CI)	Subtotals only
5.1 End of trial at immediate time point (12 weeks)	3	392	Std. Mean Difference (Random, 95% CI)	-1.01 [-2.54, 0.53]

### Comparison 2. Computerised cognition-based training versus inactive control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Episodic memory	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Short time point (12 weeks to 1 year)	1	150	Mean Difference (IV, Random, 95% CI)	-0.90 [-1.73, -0.07]
2 Speed of processing	2		Std. Mean Difference (Random, 95% CI)	Subtotals only
2.1 End of trial at immediate time point (12 weeks)	2	204	Std. Mean Difference (Random, 95% CI)	-0.28 [-0.82, 0.26]
3 Executive function	2		Std. Mean Difference (Random, 95% CI)	Subtotals only
3.1 End of trial	2	292	Std. Mean Difference (Random, 95% CI)	-0.08 [-0.31, 0.15]
3.2 Immediate time point (12 weeks)	1	144	Std. Mean Difference (Random, 95% CI)	-0.03 [-0.35, 0.30]
3.3 Short time point (12 weeks to 1 year)	1	148	Std. Mean Difference (Random, 95% CI)	-0.13 [-0.45, 0.20]
4 Working memory	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 End of trial at immediate time point (12 weeks)	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.43, 0.27]
5 Verbal fluency	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

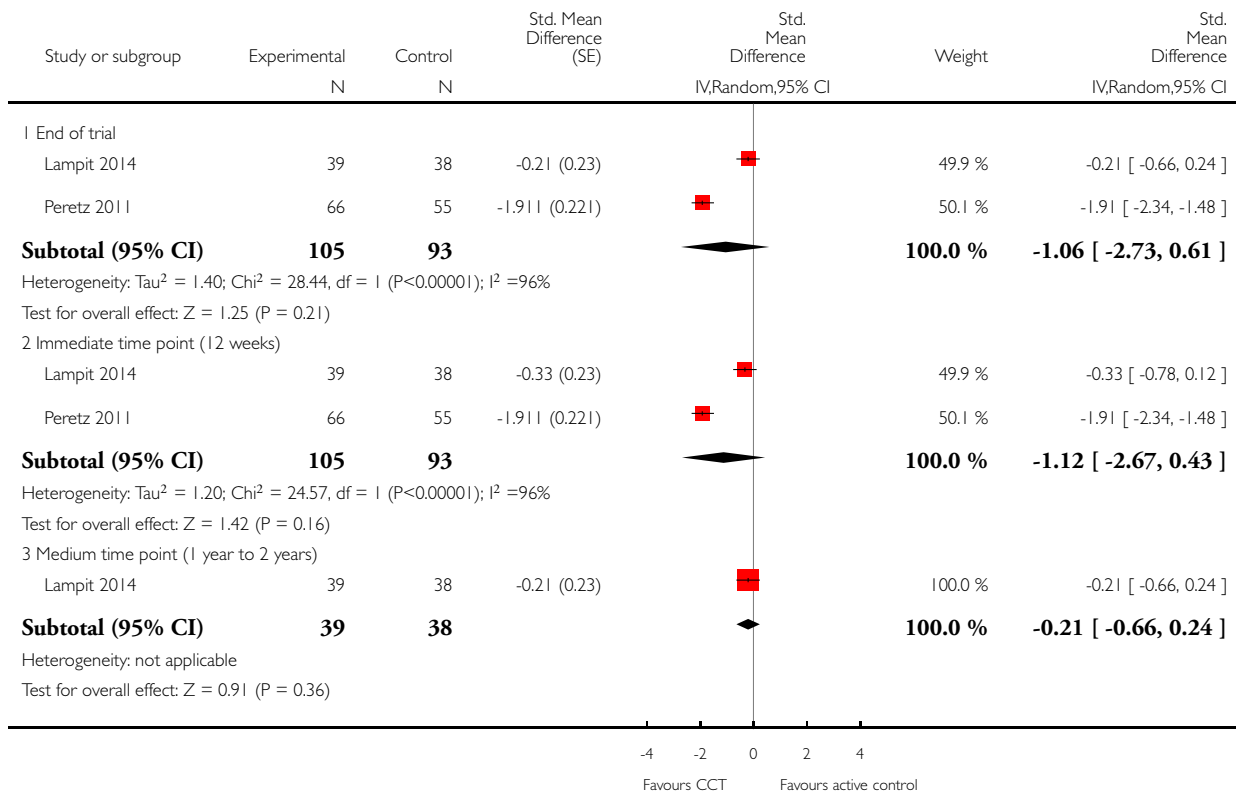
5.1 Short time point (12 weeks to 1 year)	1	150	Mean Difference (IV, Random, 95% CI)	-0.11 [-1.58, 1.36]
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### Analysis 1.1. Comparison 1 Computerised cognition-based training versus active control, Outcome 1 Global cognitive function.

Review: Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life

Comparison: 1 Computerised cognition-based training versus active control

Outcome: 1 Global cognitive function

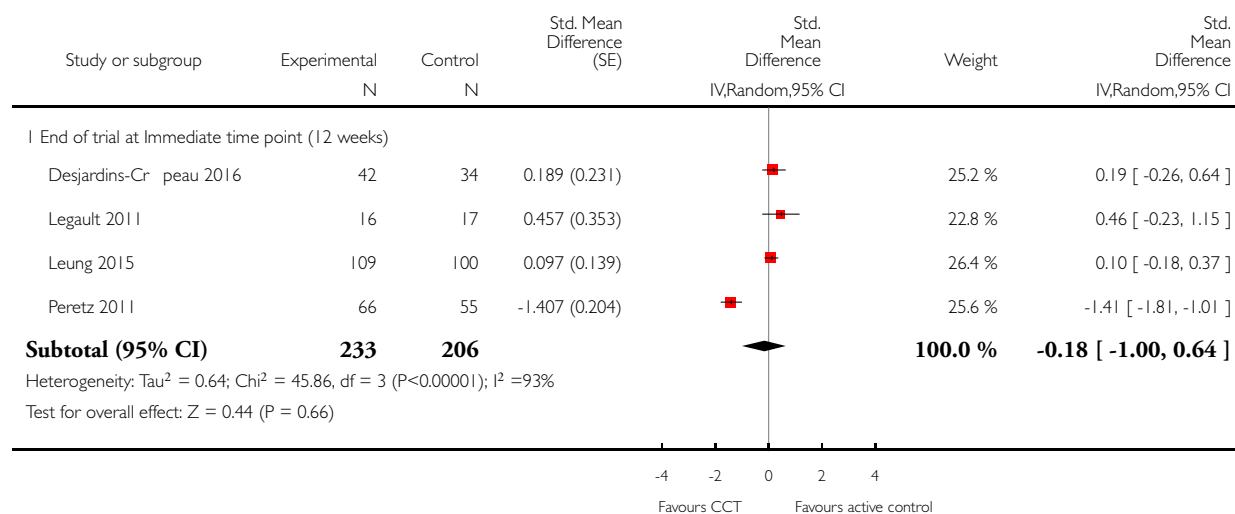


## Analysis 1.2. Comparison 1 Computerised cognition-based training versus active control, Outcome 2 Episodic memory.

Review: Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life

Comparison: 1 Computerised cognition-based training versus active control

Outcome: 2 Episodic memory

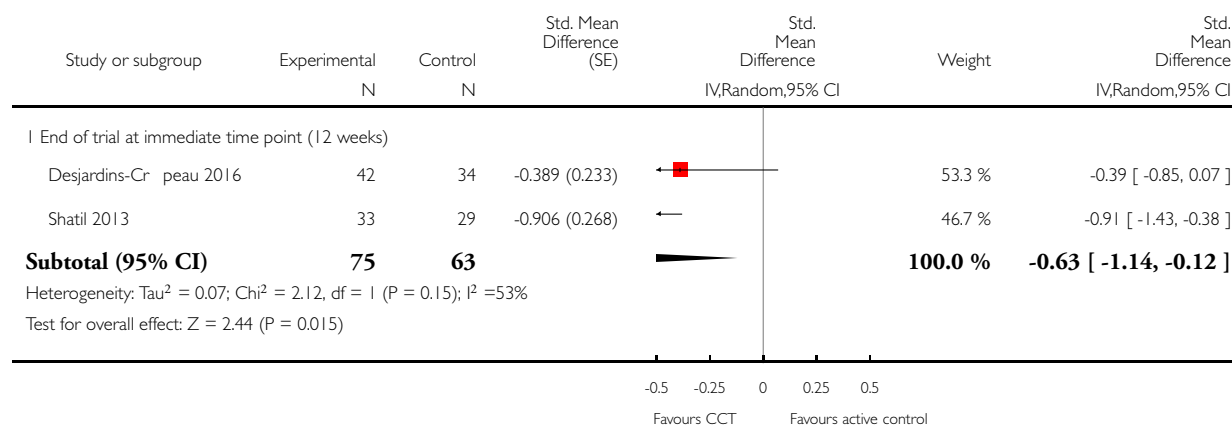


### Analysis 1.3. Comparison 1 Computerised cognition-based training versus active control, Outcome 3 Speed of processing.

Review: Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life

Comparison: 1 Computerised cognition-based training versus active control

Outcome: 3 Speed of processing



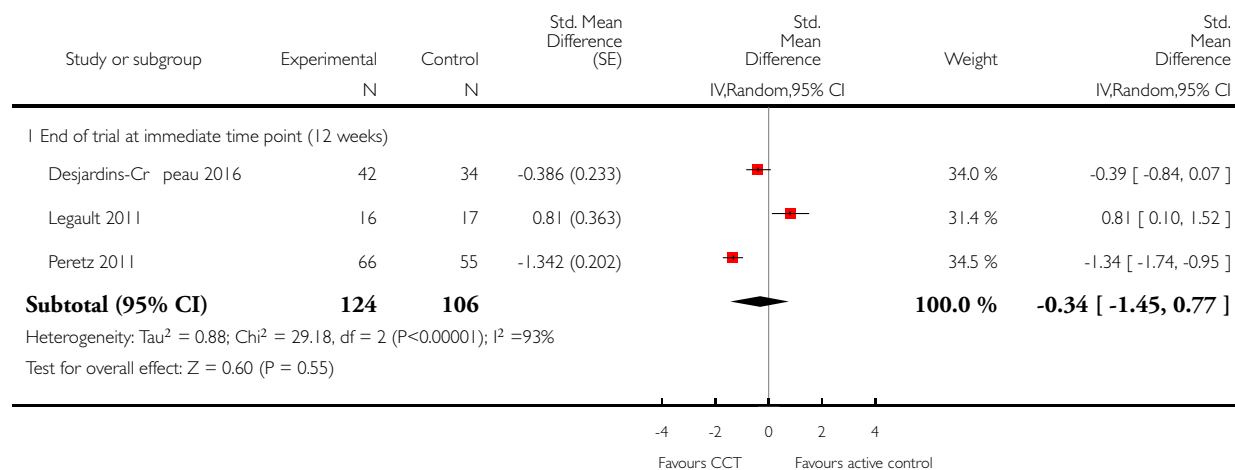


#### Analysis 1.4. Comparison 1 Computerised cognition-based training versus active control, Outcome 4 Executive function.

Review: Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life

Comparison: 1 Computerised cognition-based training versus active control

Outcome: 4 Executive function

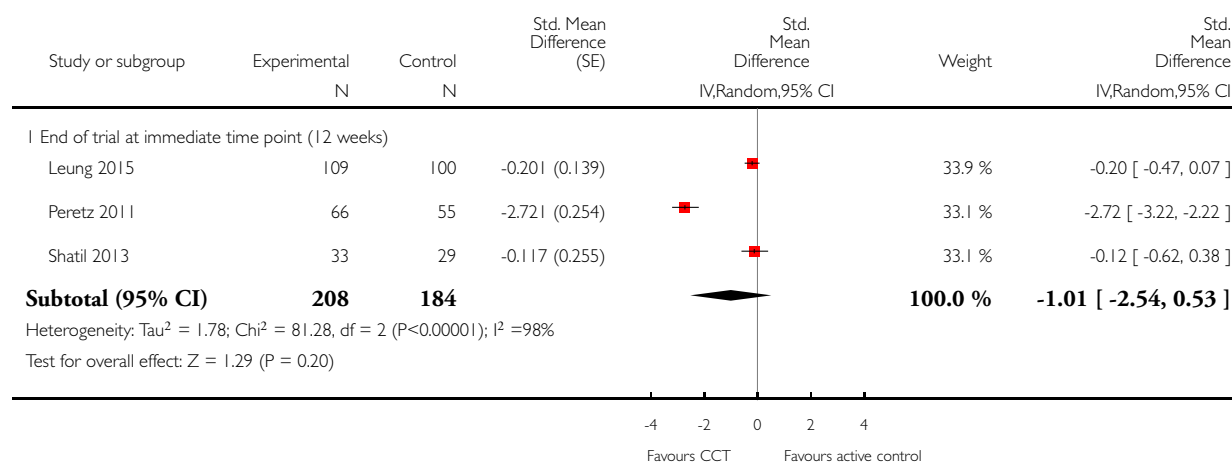


### Analysis 1.5. Comparison 1 Computerised cognition-based training versus active control, Outcome 5 Working memory.

Review: Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life

Comparison: 1 Computerised cognition-based training versus active control

Outcome: 5 Working memory

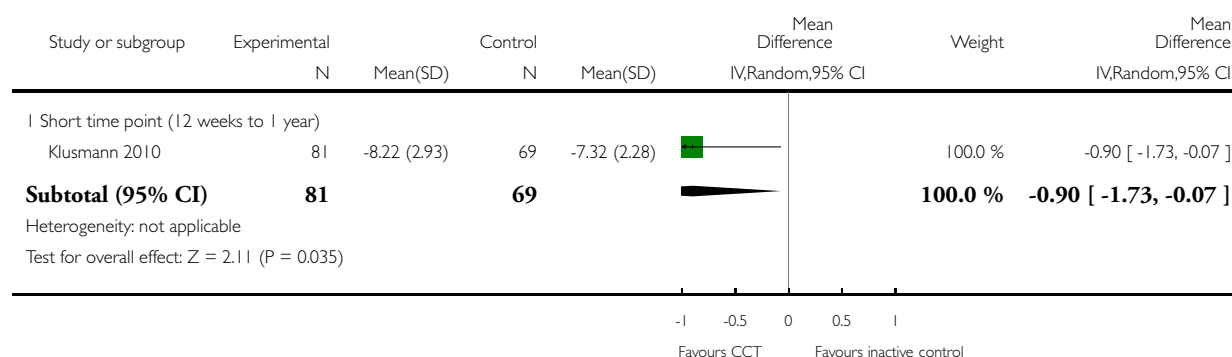


### Analysis 2.1. Comparison 2 Computerised cognition-based training versus inactive control, Outcome 1 Episodic memory.

Review: Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life

Comparison: 2 Computerised cognition-based training versus inactive control

Outcome: 1 Episodic memory

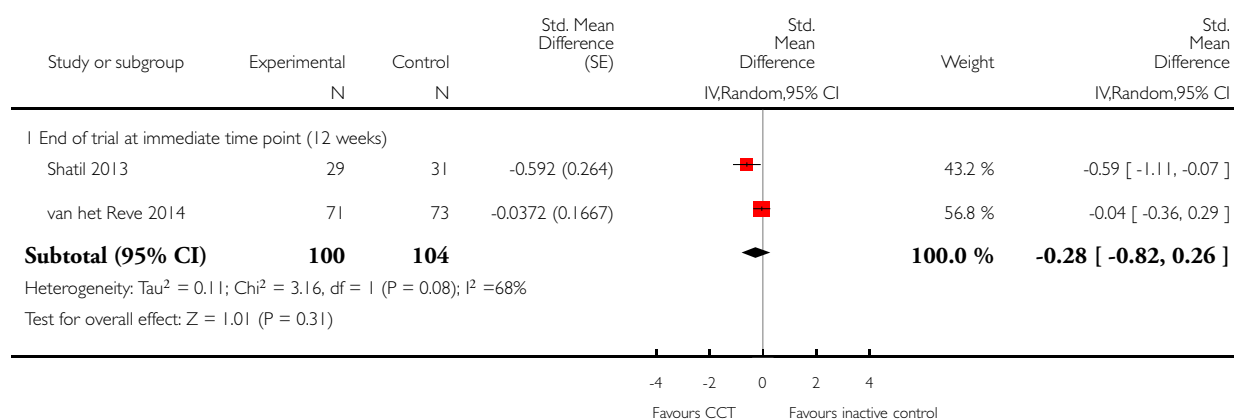


## Analysis 2.2. Comparison 2 Computerised cognition-based training versus inactive control, Outcome 2 Speed of processing.

Review: Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life

Comparison: 2 Computerised cognition-based training versus inactive control

Outcome: 2 Speed of processing

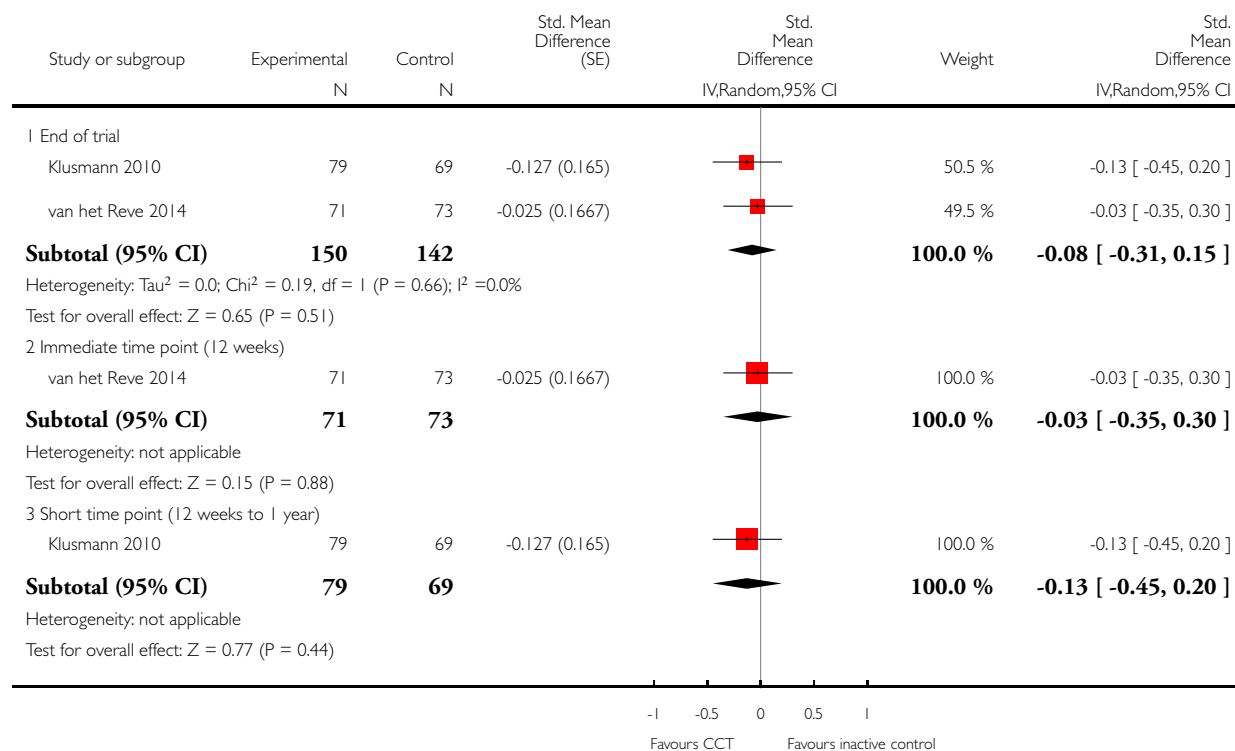


### Analysis 2.3. Comparison 2 Computerised cognition-based training versus inactive control, Outcome 3 Executive function.

Review: Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life

Comparison: 2 Computerised cognition-based training versus inactive control

Outcome: 3 Executive function

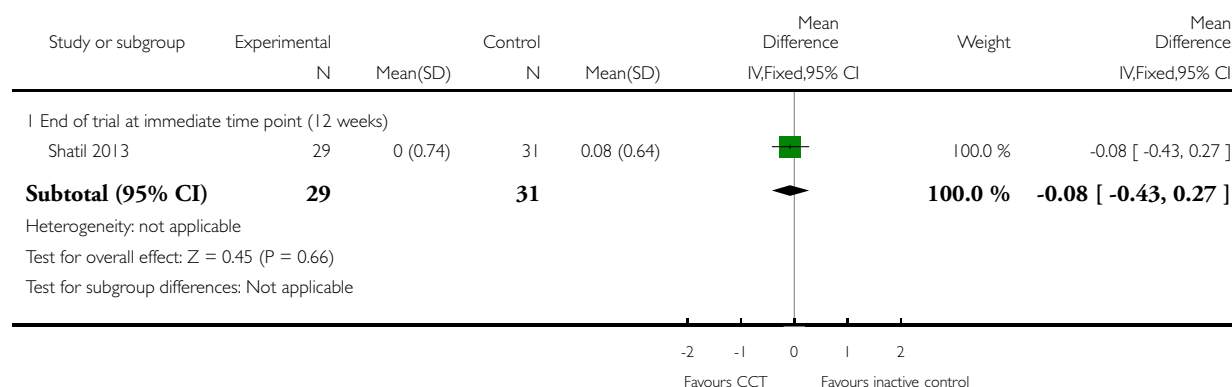


## Analysis 2.4. Comparison 2 Computerised cognition-based training versus inactive control, Outcome 4 Working memory.

Review: Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life

Comparison: 2 Computerised cognition-based training versus inactive control

Outcome: 4 Working memory

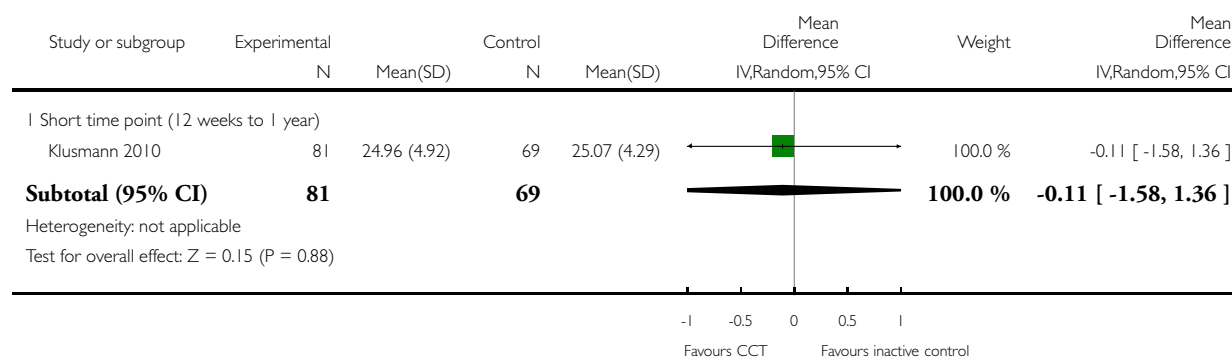


## Analysis 2.5. Comparison 2 Computerised cognition-based training versus inactive control, Outcome 5 Verbal fluency.

Review: Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life

Comparison: 2 Computerised cognition-based training versus inactive control

Outcome: 5 Verbal fluency



## APPENDICES

### Appendix I. Sources searched and search strategies

Source	Search strategy	Hits retrieved
ALOIS ( <a href="http://www.medicine.ox.ac.uk/alois">www.medicine.ox.ac.uk/alois</a> ) [Date of most recent search: 31 March 2018]	Basic search: COG [Studies within ALOIS are coded COG if the intervention is a cognitive-based intervention]	Jan 2015: 31 Jul 2015: 4 Feb 2016: 2 Jul 2016: 0 Mar 2018: 0
MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP) [Date of most recent search: 31 March 2018]	<ol style="list-style-type: none"> <li>1. "cognitive stimulation".ti,ab.</li> <li>2. cognitive ADJ3 train*.ti,ab.</li> <li>3. "cognitive exercis*".ti,ab.</li> <li>4. "brain train".ti,ab.</li> <li>5. (memory adj3 train*).ti,ab.</li> <li>6. "memory rehab*".ti,ab.</li> <li>7. "memory enhance*".ti,ab.</li> <li>8. "poetry-based stimulation".ti,ab.</li> <li>9. "cognitive flexibility".ti,ab.</li> <li>10. "brain exercis*".ti,ab.</li> <li>11. "cognitive rehab*".ti,ab.</li> <li>12. "mnemonic train".ti,ab.</li> <li>13. CST.ti,ab.</li> <li>14. (mental adj3 activit*).ti,ab.</li> <li>15. "cognitive intervention*".ti,ab.</li> <li>16. "cognitive motor intervention*".ti,ab.</li> <li>17. "cognition based intervention*".ti,ab.</li> <li>18. "cognitive enrich*".ti,ab.</li> <li>19. Cognitive Therapy/ mt</li> <li>20. or/1-19</li> <li>21. *aging/</li> <li>22. Aged</li> <li>23. "Aged, 80 and over"</li> <li>24. Middle Aged</li> <li>25. Age Factors</li> <li>26. *Cognition/</li> <li>27. *Cognition Disorders/</li> <li>28. Memory/</li> <li>29. Memory Disorders/</li> <li>30. Brain/</li> <li>31. Mild Cognitive Impairment/</li> <li>32. Executive Function/</li> <li>33. (cognit* ADJ3 (func* OR declin* OR reduc* OR impair* OR improve* OR deficit* OR progress* 34. OR perform*)).ti,ab</li> <li>35. "mental perform*".ti,ab.</li> </ol>	Jan 2015: 1455 Jul 2015: 70 Feb 2016: 303 Jul 2016: 423 Mar 2018: 489

(Continued)

	36. memory.ti,ab. 37. "executive function*".ti,ab. 38. MCI.ti,ab. 39. AAMI.ti,ab. 40. ACMI.ti,ab. 41. ARCD.ti,ab. 42. CIND.ti,ab. 43. (nMCI OR aMCI OR mMCI OR MCIa).ti,ab. 44. Dementia/ 45. Alzheimer Disease/ 46. dement*.ti,ab. 47. alzheimer*.ti,ab. 48. "old* age*".ti,ab. 49. elderly.ti,ab. 50. "middle age*".ti,ab. 51. "old*adults".ti,ab. 52. seniors.ti,ab. 53. "senior citizens".ti,ab. 54. "community dwelling".ti,ab. 55. pensioners.ti,ab. 56. or/21-55 57. randomized controlled trial.pt. 58. controlled clinical trial.pt. 59. randomized.ab. 60. placebo.ab. 61. drug therapy.fs. 62. randomly.ab. 63. trial.ab. 64. groups.ab. 65. or/57-64 66. exp animals/ not humans.sh. 67. 65 NOT 66 68. 67 AND 56 AND 20 [all results] 69. ("cognitive stimulation" OR "cognitive training").ti. 70. *Cognition 71. *Aging/ 72. and/69-71 73. 72 AND 57 [ <b>'no brainer' results - directly sent to core author team</b> ] 74. 68 NOT 73 [ <b>results minus 'no brainer' results - for the crowd to screen</b> ]	
Embase 1974-24 January 2018 (Ovid SP) [Date of most recent search: 31 March 2018]	1. aging/ 2. aged/ 3. middle aged/ 4. mild cognitive impairment/ 5. elderly.ti,ab. 6. MCI.ti,ab.	Jan 2015: 1289 Jul 2015: 163 Feb 2016: 380 Jul 2016: 268 Mar 2018: 640

(Continued)

	<p>7. AAMI.ti,ab.  8. ACMI.ti,ab.  9. ARCD.ti,ab.  10. CIND.ti,ab.  11. (nMCI or aMCI or mMCI or MCla).  ti,ab.  12. "old* age*".ti,ab.  13. elderly.ti,ab.  14. "middle age*".ti,ab.  15. "old* aadults".ti,ab.  16. seniors.ti,ab.  17. "senior citizens".ti,ab.  18. "community dwelling".ti,ab.  19. pensioners.ti,ab.  20. ("aged sample" or "aged population" or  "older sample" or "older population").ti,ab  21. "CDR 0.5".ti,ab.  22. (cognit* adj3 (func* or declin* or re-  duc* or impair* or improve* or deficit* or  progress* or perform* or abilit*)).ti,ab  23. or/1-22  24. *cognition/  25. memory/ or episodic memory/  26. executive function/  27. attention/  28. "mental perform*".ti,ab.  29. memory.ti,ab.  30. dementia/  31. Alzheimer disease/  32. dement*.ti,ab.  33. alzheimer*.ti,ab.  34. or/24-33  35. randomized controlled trial/  36. controlled clinical trial/  37. (randomly adj2 allocat*).ab.  38. (randomly adj2 divide*).ab.  39. randomi?ed.ab.  40. (controlled adj7 (study or design or  trial)).ti,ab.  41. "double-blind*".ti,ab.  42. "single blind*".ti,ab.  43. groups.ab.  44. or/35-43  45. "cognitive stimulation".ti,ab.  46. (cognitive adj3 train*).ti,ab.  47. "cognitive exercis*".ti,ab.  48. "brain train*".ti,ab.  49. (memory adj3 train*).ti,ab.</p>	
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(Continued)

	50. "memory enhance*".ti,ab. 51. "memory rehab*".ti,ab. 52. "brain exercis*".ti,ab. 53. "cognitive rehab*".ti,ab. 54. "cognitive rehab*".ti,ab. 55. "mnemonic train*".ti,ab. 56. CST.ti,ab. 57. (mental adj3 activit*).ti,ab. 58. "cognitive intervention*".ti,ab. 59. "cognitive motor intervention*".ti,ab. 60. "cognition based intervention*".ti,ab. 61. "cognitive enrich*".ti,ab. 62. "reality orientation".ti,ab. 63. (memory adj2 game*).ti,ab. 64. or/45-63 65. 23 and 34 and 44 and 64 66. ("cognitive stimulation" or "cognitive training").ti,ab. 67. cognition/ 68. (MCI or "mild cognitive impairment" or elderly or "old* adults" or "middle age*") .ti 69. 66 and 67 and 68 70. 35 and 69 71. 65 not 70	
PSYCINFO 1806-January week 2 2018 (Ovid SP) [Date of most recent search: 31 March 2018]	1. exp Aging/ 2. exp Cognitive Impairment/ 3. "cognit* impair*".ti,ab. 4. MCI.ti,ab. 5. AAMI.ti,ab. 6. ACMI.ti,ab. 7. ARCD.ti,ab. 8. CIND.ti,ab. 9. (nMCI or aMCI or mMCI or MCIa).ti,ab. 10. "old* age*".ti,ab. 11. elderly.ti,ab. 12. "middle age*".ti,ab. 13. "old* adults".ti,ab. 14. seniors.ti,ab. 15. "senior citizens".ti,ab. 16. "community dwelling".ti,ab. 17. pensioners.ti,ab. 18. or/1-17 19. randomi?ed.ti. 20. (randomly adj2 allocat*).ab. 21. (randomly adj2 divide*).ab. 22. RCT.ti,ab.	Jan 2015: 166 Jul 2015: 20 Feb 2016: 25 Jul 2016: 12 Mar 2018: 70

(Continued)

	23. "double-blind*".ti,ab. 24. "single blind*".ti,ab. 25. "randomi?ed trial".ab. 26. "randomi?ed control* trial".ab. 27. "random allocation".ab. 28. "controlled clinical trial".ti,ab. 29. (controlled adj4 (study or design or trial)).ti,ab. 30. or/19-29 31. "cognitive stimulation".ti,ab. 32. (cognitive adj3 train*).ti,ab. 33. "cognitive exercis*".ti,ab. 34. "brain train*".ti,ab. 35. (memory adj3 train*).ti,ab. 36. "memory enhance*".ti,ab. 37. "memory rehab*".ti,ab. 38. "brain exercis*".ti,ab. 39. "cognitive rehab*".ti,ab. 40. "cognitive rehab*".ti,ab. 41. "mnemonic train*".ti,ab. 42. CST.ti,ab. 43. (mental adj3 activit*).ti,ab. 44. "cognitive intervention*".ti,ab. 45. "cognitive motor intervention*".ti,ab. 46. "cognition based intervention*".ti,ab. 47. "cognitive enrich*".ti,ab. 48. "reality orientation".ti,ab. 49. (memory adj2 game*).ti,ab. 50. or/31-49 51. 18 and 30 and 50 52. *Cognition/ 53. (MCI or "mild cognitive impairment" or elderly or "old* adults" or "middle age*") .ti 54. ("cognitive stimulation" or "cognitive training").ti,ab. 55. 19 or 20 or 21 56. 52 and 53 and 54 and 55 57. 51 not 56	
CINAHL (EBSCOhost) [Date of most recent search: 31 March 2018]		Jan 2015: 390 Jul 2015: 13 Feb 2016: 57 Jul 2016: 12 Mar 2018: 125
ISI Web of Science [includes: Web of Science (1945-present); BIOSIS Previews (1926-present); MEDLINE (1950-present); Journal Citation Reports]; BIO-	("mild cognitive impairment" OR elderly OR "age* subjects" OR "old* adult*" OR "middle age*" OR MCI) AND TOPIC: ("randomly allocated" OR "random alloca-	Jan 2015: 333 Jul 2015: 44 Feb 2016: 108 Jul 2016: 35

(Continued)

SIS Previews [Date of most recent search: 31 March 2018]	tion" OR randomised OR randomized OR RCT OR "controlled trial" OR "double blind" OR "single blind") AND TOPIC: ("cognit* stim*" OR "cognit* train*" OR puzzle OR "brain train*" OR "cognit* exercis*" OR "brain exercis*" OR "memory exercis*" OR "brain gam*" OR "cognit* gam*" OR "memory gam*" OR sudoku OR crossword* OR "reality orientation") AND TOPIC: (cognition OR dementia OR memory OR "executive function" OR alzheimer*) Timespan: All years. Search language=Auto	Mar 2018: 268
LILACS (BIREME) [Date of most recent search: 31 March 2018]		Jan 2015: 4 Jul 2015: 0 Feb 2016: 0 Jul 2016: 0 Mar 2018: 0
CENTRAL (via CRSO) [Date of most recent search: 31 March 2018]	#1 MeSH descriptor: [Aged, 80 and over] explode all trees #2 MeSH descriptor: [Aged] explode all trees #3 MeSH descriptor: [Middle Aged] explode all trees #4 MeSH descriptor: [Mild Cognitive Impairment] explode all trees #5 "cognit* impair*" or MCI #6 elderly #7 "old* adults" #8 "old* age*" #9 "old* sample" #10 senior citizens #11 pensioners #12 seniors #13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 #14 MeSH descriptor: [Cognition] explode all trees #15 MeSH descriptor: [Dementia] explode all trees #16 cognit* #17 memory #18 "executive function*" #19 processing #20 "mental perform*" #21 dement*	Jan 2015: 274 Jul 2015: 11 Feb 2016: 57 Jul 2016: 4 Mar 2018: 125

(Continued)

	#22 alzheimer* #23 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 #24 "cognitive stimulation" #25 "cognitive training" #26 "brain train*" #27 "brain gam*" #28 "memory train*" or "memory game*" #29 puzzle* #30 crossword* #31 sudoku* #32 "mental game*" #33 "mental agil*" #34 "cognitive exercis*" #35 "mental exercis*" #36 #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 #37 #13 and #23 and #36	
Clinicaltrials.gov ( <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a> ) [Date of most recent search: 31 March 2018]		Jan 2015: 17 Jul 2015: 4 Feb 2016: 2 Jul 2016: 0 Mar 2018: 4
ICTRP Search Portal ( <a href="http://apps.who.int/trialsearch">http://apps.who.int/trialsearch</a> ) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrials.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry - India; Clinical Research Information Service - Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register] [Date of most recent search: 31 March 2018]		Jan 2015: 22 Jul 2015: 3 Feb 2016: 1 Jul 2016: 0 Mar 2018: 4
TOTAL before de-duplication		Jan 2015: 3981 Jul 2015: 332 Feb 2016: 935 Jul 2016: 754 Mar 2018: 1725 <b>TOTAL: 7727</b>
TOTAL after de-duplication		<b>TOTAL: 5832</b>

(Continued)

TOTAL after first assessment by the Crowd and CDCIG Information Specialists	Jan 2015: 604 Jul 2015: 60 Feb 2016: 164 Jul 2016: 73 Mar 2018: 189 <b>TOTAL: 1090</b>
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## Appendix 2. Definitions of design, patient, and intervention characteristics as applied in the stratified analyses exploring between-trial variations in intervention effects

Item	Definition
<i>Design-related characteristics*</i>	
Concealment of allocation (avoiding selection bias)	Guidance from the <i>Cochrane Handbook for Systematic Reviews of Interventions</i> will be used to judge bias related to sequence generation and concealment of allocation using the 2 Cochrane 'Risk of bias' items ( <a href="#">Higgins 2011</a> ). From these, the statistician will derive a single variable to be used in the stratified analysis: allocation concealment will be judged at low risk of bias if the investigators responsible for patient selection were unable to suspect, before allocation, which treatment was next. Concealment will be downgraded to high risk of bias if there is evidence of inadequate sequence generation ( <a href="#">Rutjes 2012</a> )
Blinding of patients and personnel (avoiding performance bias)	Low risk of bias will be judged: <ul style="list-style-type: none"> <li>• if a credible sham procedure was used; or if a placebo supplement or pill was used that was reported to be identical in appearance from the experimental intervention, and the specific outcome or group of outcomes is/are likely to be influenced by lack of blinding; or</li> <li>• if blinding is absent or suboptimal and the specific outcome, such as mortality, is not likely to be influenced by lack of blinding</li> </ul>
Blinding of outcome assessment (avoiding detection bias)	<i>For self-reported/partner-reported outcomes</i> Low risk of bias will be judged if: <ul style="list-style-type: none"> <li>• self-report outcomes were assessed AND blinding of patients was considered adequate AND there was no information to suggest that there was an investigator involved during the process of outcome assessment; OR if blinding of investigators performing the outcome assessment was reported AND an attempt to blind patients was reported</li> </ul> <i>For other outcomes</i> <ul style="list-style-type: none"> <li>• Outcome assessment was considered to be blinded if the outcome assessment was reported to be blinded</li> </ul>

(Continued)

Statistical analyses (avoiding attrition bias)	<p><i>For continuous outcomes</i></p> <p>Low risk of bias will be judged if:</p> <ul style="list-style-type: none"> <li>at least 90% of randomised participants were analysed AND the difference in percentage of participants not analysed was 5% or lower across trial arms; or</li> <li>for trials using imputations to handle missing data: the percentage of participants with missing data did not exceed 20% AND the difference in percentage of participants with imputed data was 5% or lower across trial arms AND applied imputation methods were judged to be appropriate. Multiple imputation techniques will be considered appropriate, and simple methods such as “last observation carried forward” or “baseline carried forward” will be considered inappropriate</li> </ul> <p><i>For binary outcomes of rare events</i></p> <p>Low risk of bias will be judged if:</p> <ul style="list-style-type: none"> <li>the event rate is low (e.g. incidence of dementia) AND at least 95% of randomised participants were analysed AND there is no evidence of differential reasons for missing data that may alter the estimate AND the rate of missing data does not exceed the expected event rates</li> </ul> <p><i>For binary outcomes of non-rare events</i></p> <p>Low risk of bias will be judged if:</p> <ul style="list-style-type: none"> <li>at least 90% of randomised participants were analysed AND the difference in percentage of participants not analysed was 5% or lower across trial arms AND there is no evidence of differential reasons for missing data that may alter the estimate AND the rate of missing data does not exceed the expected event rates</li> </ul>
Trial size	The cut-off to distinguish small from larger trials will be determined by a sample size calculation on the primary outcome
Publication status	Full journal article vs other type or unpublished material
Follow-up duration	For the cognitive outcomes, we will group studies according to these follow-up cut-offs to describe immediate results (up to 12 weeks), short-term (up to 1 year), medium-term (1 to 2 years), and longer-term results (more than 2 years)
<b><i>Treatment-related characteristics</i></b>	
Treatment and control Treatment duration	<p>The analyses will be stratified by:</p> <ul style="list-style-type: none"> <li>control intervention (placebo vs no intervention vs usual care, where no intervention refers to RCTs with standardised concurrent treatments in both experimental and control arms);</li> <li>training in multiple domains (yes/no); or</li> <li>mode of delivery <ul style="list-style-type: none"> <li>training supervision (yes /no); or</li> <li>group training (yes/no)</li> </ul> </li> </ul> <p>The analyses will be stratified into &gt; 3 sessions per week (yes/no)</p>

(Continued)

	, length of training sessions > 30 minutes (yes/no) based upon previous findings (Lampit 2014) and total number of sessions The minimum treatment duration of 3 months is considered short-term, 3 to 12 months as medium-term, and 12 months as long-term
<b>Participant-related characteristics</b>	
Participant-related criteria	Gender, level of education (in years)
* The descriptions depicted in this Table are provided in addition to the guidance available in the <i>Cochrane Handbook for Systematic Reviews of Interventions</i> (Higgins 2011). Stratified analyses are performed only for the primary outcome and only if about 10 RCTs contribute to the analyses	

## CONTRIBUTIONS OF AUTHORS

Completion of the protocol: Nicola Gates, Anne Rutjes, Marcello Di Nisio, Salman Karim, Jennifer Ware, Lee Yee Chong, Evrim March, Robin Vernooij.

Screening of references: Students For Best Evidence (title/abstract screening).

Full-text screening: Nicola Gates, Salman Karim, Evrim March, Robin Vernooij, Gabriel Martínez.

Acquisition of data: Nicola Gates, Anne Rutjes, Marcello Di Nisio, Salman Karim, Evrim March, Robin Vernooij, Gabriel Martínez.

Risk of bias assessments: Nicola Gates, Anne Rutjes, Marcello Di Nisio, Salman Karim, Evrim March, Robin Vernooij, Gabriel Martínez.

SoF and GRADE-ING: Robin Vernooij (SoF and GRADE-ING), Anne Rutjes (SoF).

Statistical analysis: Anne Rutjes.

Overall interpretation of data: Nicola Gates, Anne Rutjes, Marcello Di Nisio, Evrim March, Robin Vernooij, Gabriel Martínez.

Manuscript preparation: Nicola Gates, Anne Rutjes, Robin Vernooij, Gabriel Martínez.

## DECLARATIONS OF INTEREST

Nicola J Gates: none known.

Anne WS Rutjes: Dr. Rutjes declares partial funding by a grant for the project 'OPERAM: OPTimising therapy to prevent Avoidable hospital admissions in the Multi-morbid elderly' supported by the European Union's Horizon 2020 research and innovation programme under the grant agreement No 6342388, and by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 15.0137.

Marcello Di Nisio: Di Nisio declares partial funding by a grant for the project 'OPERAM: OPTimising therapy to prevent Avoidable hospital admissions in the Multi-morbid elderly' supported by the European Union's Horizon 2020 research and innovation programme under the grant agreement No 6342388. Di Nisio reports participation to Advisory Boards for Daiichi-Sankyo, Aspen, and Pfizer, and consultancy fees for Daiichi-Sankyo, Bayer Health Care, and Leo Pharma outside the submitted work.

Salman Karim: none known.

Lee-Yee Chong: none known.

Evrin March: none known.

Gabriel Martínez: none known.

Robin WM Vernooij: none known.

## SOURCES OF SUPPORT

### Internal sources

- No sources of support supplied

### External sources

- National Institute for Health Research (NIHR), UK.

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- SERI and Horizon 2020, Other.

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

[Appendix 2](#) describes the features we planned to use in stratified analyses to explore between-trial heterogeneity. We also planned to explore bias associated with small study size, such as publication bias, in funnel plot analyses. As our protocol required the inclusion of 10 trials for such analyses to be meaningful, we omitted stratified and funnel plot analyses. We also omitted the protocol-defined sensitivity analysis for the primary outcome. Latter analyses would include high-quality trials only, with high quality planned to be defined using results of the stratified analyses. As stratified analyses could not be performed, we omitted this sensitivity analyses. We also planned to perform sensitivity analyses according to the definitions used for MCI or dementia, namely, restricting analyses to trials applying internationally accepted definitions. As none of the trials reported such outcomes, we could not perform any analyses for this patient relevant outcome. We used a hierarchy to select instruments from which we would analyse the outcome data. We made the decision to use the hierarchy before we began to extract data.